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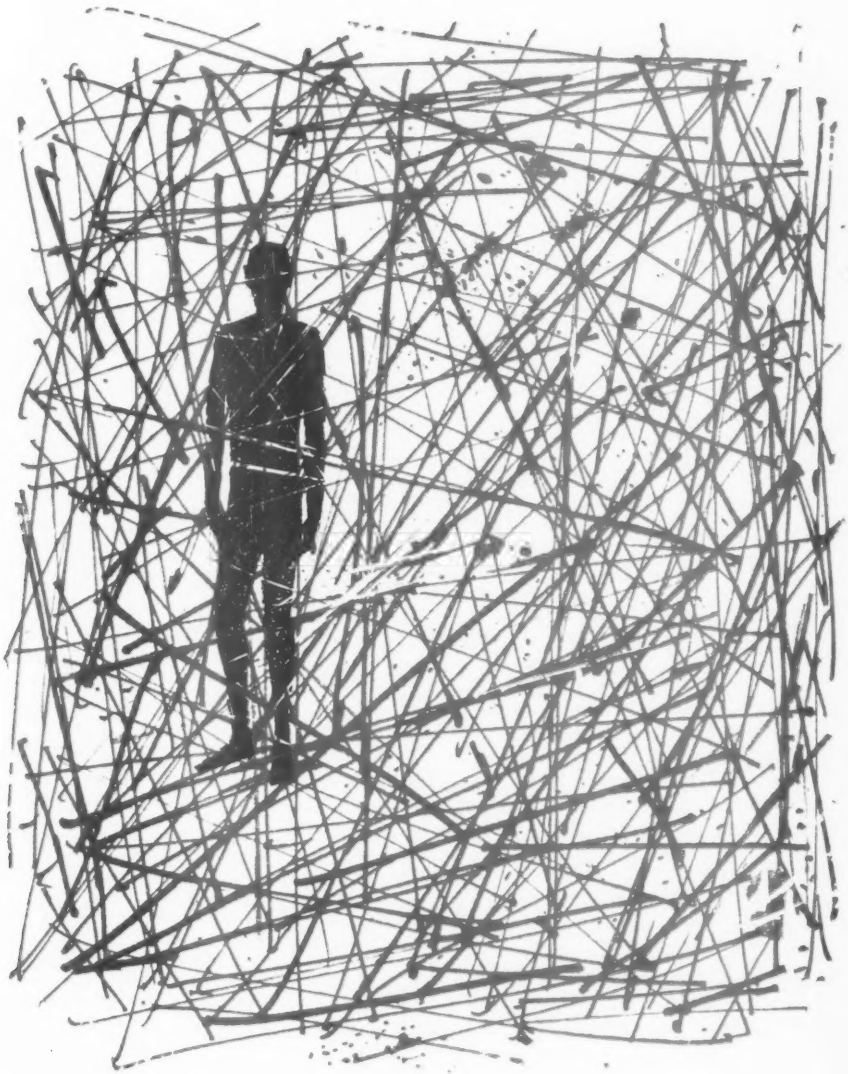

SUMMER 1964

The New Biology and The Nature of Man

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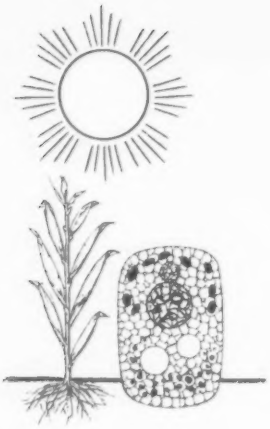

AGRICULTURAL SCIENCE REVIEW

Summer 1964 Vol II No. 3

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EDITOR: WARD W. KONKLE

The Molecular Level of Science

The pace of understanding is quickening for many processes of life—the manner of photosynthesis, the nature of vision, and the seasonal adaptations of animals and plants as light-dependent phenomena.

Much of this understanding stems from knowledge gained at the molecular level. Pathways of biosynthesis, the molecular basis of heredity, the functioning of insect hormones and sex attractants, interconnecting and controlling links of metabolism, and the nature of information storage in the brain—all are examples of understanding gained through deliberate study of small-scale phenomena. From such studies we are developing a better understanding of the origin of life in man and maize, and of population pressure in the open and in the flour barrel.

Going deeper into the causes of this quickening pace, we cannot ignore the long accumulation of knowledge, the small bits of information that by themselves seem to have little meaning, yet which add significantly to our treasury of knowledge.

The refinement of tools and the supply of materials likewise contribute to progress in understanding. Under the micromethod approach, 0.001 ml today serves the purpose of 1.0 ml yesterday and a microgram is a large quantity. Optical instruments and resonance devices are at hand to scan in a moment molecular properties that once required weeks to measure or were unknown. Hopeless mixtures are resolved by chromatography. The isotope is ubiquitous for minute tracing.

Without these things and others, the pace would be much slower. The mind is left unfettered for its nobler purpose of developing inviting avenues of study and research.

STERLING B. HENDRICKS, *Chief Scientist, Mineral Nutrition Laboratory, Agricultural Research Service*

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The New Biology and the Nature of Man

George W. Beadle

Agricultural Science Review is privileged to reprint in this issue an outstanding paper[1] *about the prime source of genetic information—DNA—within which lie the specifications for all living organisms from viruses to man. Originally delivered as the third Annual Dewey F. Fagerburg Lecture sponsored by The Michigan Memorial-Phoenix Project, Dr. Beadle's paper embraces a significant area among the agricultural sciences, particularly those disciplines entrusted with maintaining man's renewable resources. The text is based on the transcript of the lecture, which Dr. Beadle delivered informally from notes; hence the conversational style.*

In one sense I might say I begin this talk with the humanities, for I start with the consideration of the oldest living language. It is at least 3 billion years old, and a remarkable language it is. It exists only in written form, that is, "written" in submicroscopic molecular code. It is remarkably simple, for it has only four letters. Each of these is one two-hundred-millionth of an inch across. Each is made of but five kinds of atoms—carbon, hydrogen, oxygen, nitrogen, and phosphorus—and there are only about 32 atoms in each letter. All the words in this language appear to be 3-letter words, and there are only 64 of them possible. This beats Basic English by a very wide margin. Most remarkable of all, this language is the only language known to have a built-in capacity for copying itself. There is no need for secretaries, typewriters, or printing presses.

It is a language in which the specifications for all living organisms, from viruses to man, that have ever existed on earth are written.

The number of letters in the specifications for these organisms varies from 5,000 letters for the specifications of the simplest known virus to 5 billion for the specifications of man. That's over a million-fold difference. What is the name of this language? I call it DNAese, because it is contained in deoxyribose nucleic acid molecules, which we call DNA.

DNA—DEOXYRIBONUCLEIC ACID

How do we know that DNA carries the specifications of the kind I have said? The answer is very

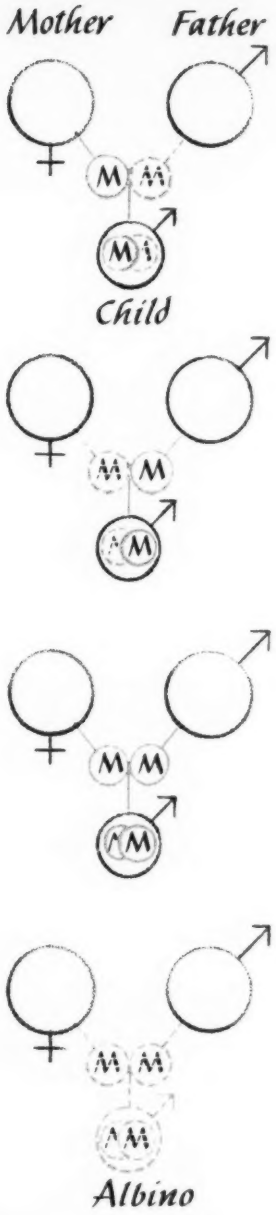
[1] Reprinted from *Phoenix*, Vol. 2, No. 1, 1963, published by The Michigan Memorial-Phoenix Project of the University of Michigan by permission of the publisher and the author. Copyright 1963 by The Michigan Memorial-Phoenix Project. Original artwork by Leonard Zamiska.

simple. In viruses—some viruses at least—one can strip away all of the components except the DNA, inflict a living cell of the proper kind with the DNA and reconstruct another generation of viruses. This means that whatever specifies the unique properties of the virus must be carried in the DNA. The same is true with bacteria. It is possible to take DNA molecules out of a bacterium in the purest possible form, transfer these molecules to another bacterium and alter the genetic specifications that say what the recipient bacterium is going to do. Now, viruses are known to have genes that are transmitted in essentially the same way that our genes are transmitted. Since only DNA is transmitted from generation to generation, the genes must be made of this substance. We don't know this directly in our own case, but we believe it is so in us, too.

What do we want to know about the language in which these specifications are written? First of all, we would like to know how we get these specifications and how we transmit them to the next generation; for this is how we receive and transmit our biological inheritances. We want to know how these specifications are written. We want to know how they are copied. We want to know how they are translated—how it is that from these specifications we can build ourselves from a single, almost microscopic, egg cell. We want to know why it is that each of us is unique. No one of us is exactly like any other person on earth—unless we happen to be a set of identical twins or triplets. Although we have common ancestors, we differ in our specifications. How did the specifications come to differ?

CLASSICAL GENETICS

First, let us talk about how we receive the specifications and how we transmit them. This you recognize immediately as classical genetics. I assume you know all about it, but I shall review it very quickly, using a characteristic in man to illustrate the point. In each of us there is an enzyme, a protein, that catalyzes one of the reactions by which melanin pigment is made. Melanin is the pigment that gives color to our hair and our eyes; it is melanin in the skin that responds to light and results in our tanning. Individuals who lack this pigment are called albinos. They are comparable to pink-eyed white rabbits in that they are unable to make melanin.



M DNA message says, "I can now make Melanin."

M DNA message says, "I can not make Melanin."

Four possible DNA messages determine whether or not a child will be an albino. If either parent sends a message that reads, "I can now make melanin," the child will not be an albino. If both parents send a message that reads, "I cannot make melanin," the child will be an albino.

Individuals unable to make melanin differ from those who make it by a single unit of their set of specifications, a unit called a gene. This particular gene comes in two forms—the form that says make a proper tyrosinase enzyme necessary for melanin synthesis and a defective form that specifies an enzyme unable to catalyze this reaction. Each of us has two representatives of this message, one from the mother, one from the father. Since the mesesage comes in two forms, there are four possible kinds of individuals. From the mother we can get a message that says, "I can now make melanin." From the father we can get one that says the same thing. Then we are pure for the message that says, "I can now make melanin." Or from the mother we can get a positive message and from the father a negative message that says, "I cannot make melanin." Because the positive message is dominant and the defective message is recessive, an individual of this kind makes melanin. Another individual may get the defective form from the mother, the active form from the father; that is, have one of each. He will also be able to make melanin. It doesn't make any difference from which parent you get the positive message. But if you get the defective message from both parents, you are pure for the message that says, "I cannot make melanin." You will be an albino.

When we pass these messages on to the next generation, one or the other goes into each of the egg or sperm cells—either the one from the mother or the one from the father. If you happen to have the capability of sending both kinds of messages, half of your children will get one form, half will get the other form. And if both parents carry both messages, then it is obvious that those who get the defective form from both parents will be albinos.

I've now given you a short course in classical genetics. Essentially, that's all there is to it, except that there are perhaps a hundred thousand other similar messages that carry their parts of the total set of instructions. If you understand how one works, you understand them all. In general biology courses and courses in genetics, we make it more complicated because we don't want to be responsible for technological unemployment of geneticists. Actually, genetics is a bit more complex if you consider all of the ramifications. For example, genes come in chromosomes; and there are many messages per chromosome. They don't always stay in the same chromosome, but can cross over into the partner or homologous chromosome.

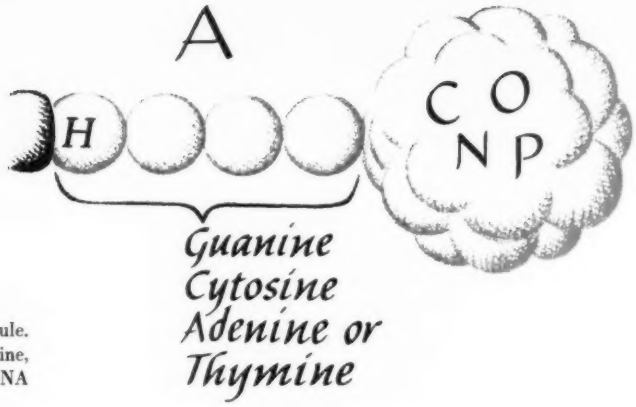
HOW DNA CARRIES INFORMATION

Now you know how hereditary messages are transmitted. Let's now consider how they are written. As I said, they are written in four "letters," which, of course, are not really letters like those of our alphabet. They are subunits of molecules—DNA molecules. We can represent these four different subunits of a DNA molecule by letters of our alphabet. To illustrate, I shall use the four letters—N, E, A, T—to represent the four molecular subunits. These units, made of 5 different atoms, average about 32 atoms per unit. Each of these units, or "letters," is about one ten-millionth of an inch across. They differ from one another in the arrangement of the atoms, not in the number of different atoms.

These DNA "letters" are arranged in long chains. One of the characteristics of this language or code is that there appears to be no spacing or punctuation between "words." It's very much simpler than ours. If I add extra letters to the sequence NEAT so that it reads NEAT-TNETAATNE—I have the beginning of a long message not unlike a DNA message.

In the nucleus of the egg cell from which we started development there are 5 billion of these "letters." If you were to take all the molecules containing the 5 billion units and string them end to end, they would form a chain about 5 feet long. But the molecules are so small in diameter that you would be unable to see the chain with the highest powered light microscope possible. The molecules can just barely be resolved with the most modern electron microscope.

How much information is contained in these 5 feet of DNA—in 5 billion units? Since there are only four letters in DNAese, to translate from it into a message of our own language would require some kind of a coding system. One system that we might use would be to have each successive three-letter unit of DNAese stand for a letter of our alphabet. If we transform the language, using the 4 letters NEAT, into a 26-letter language, we might say NEA equals A, NAE equals B, and so on,



C=carbon
H=hydrogen
N=nitrogen
O=oxygen
P=phosphorus

One letter in the chain of a DNA molecule. The base, which is either Guanine, Cytosine, Adenine or Thymine, determines the DNA letter.

until we have all 26 letters of the alphabet. In such a code we could take the 5 billion DNA "letters" of the nucleus of the egg, translate them into letters of the alphabet and then spell out a message. Since we have 5 billion units, and it takes three of them to make a letter of the alphabet, we'd end up with about 1,000,700,000 three-letter messages or letters of our alphabet. That many letters of the alphabet will make 300,000 words, 5 letters to a word. If we write out messages in all these letters in words which average 5 letters, we will get 60,000 printed pages. If we say there are 600 pages per average volume, we will have a thousand volumes. In other words, the information in the tiny microscopic nucleus, in this submicroscopic thread 5 feet long, will be the equivalent of a thousand ordinary library volumes. That is a set of genetic specifications for making one of us out of an egg cell, given a proper environment, proper raw materials, and so on.

Let's express the size of this 5-foot thread in another way. If it were wound back and forth, one layer thick, on the head of a pin, it would cover only about one-half of 1 percent of the head of the pin. That means that you could get a thousand volumes of information on half of 1 percent of the head of the pin. If you covered the whole head of the pin, you would have the equivalent of 200,000 volumes in a monolayer so thin that you could not detect it by anything less than an electron microscope. That's pretty good miniaturization. Let's go one step further. If you took all the DNA code out of all the eggs that gave rise to all the people on earth today—say 3 billion people—and wound it back and forth like cordwood, how large a stack would it make? It would make a cube an eighth of an inch on a side! Since each person requires a thousand volumes to specify him genetically, this little cube an eighth of an inch on a side is the equivalent of 3 trillion volumes of library work. In all history since the invention of the printing press, there have been printed only about 50 million different books. In this small cube we can put the equivalent of 3 trillion volumes—that's 60,000 times as much as is contained in all the books ever published.

THE MOLECULAR BASIS OF REPRODUCTION

The next question I'd like to ask is, How does this message copy itself? This is an interesting and important question because we know that every living system has somehow to send its specifications on to the next generation. In our case, from the time we get the specifications in the egg cell until the time we send them on to the next generation, we must copy the thousand volumes of information with every cell division. The number of cell divisions from the egg of one generation with which we started to the egg or the sperm which we send on to the next generation will vary with age and sex. It may be 10, 20, 30, or more successive cell divisions. This means that you must copy your specifications 10, 20, 30, or more times during your lifetime. Remember that's the equivalent of a thousand volumes with each copying. And, of course, you must not make many mistakes or the next generation won't come out right. This is the equivalent of sitting

down with a typewriter and typing a thousand volumes of information and then retyping it 10 to 30 times in succession. That's a lot of typing! We now know how this is done because of the work of a large number of people, climaxed by the discovery by James Dewey Watson and Francis H. C. Crick of the structure of the molecules that carry these four kinds of units. They discovered that these molecules are not simple single chains, but are double parallel chains that are arranged in such a way that they carry complementary information.

Now what does this mean? Opposite every T there will be an A, and conversely, the letter A will always have opposite it a T. The N will have opposite it an E, and the E will have opposite it an N. This means that if you know the order of the units in a four-letter segment you will know the order of its complementary chain. If I have the message TANE, I will have the double message T-A-N-E-/A-T-E-N-

This means that this molecule has a very simple way of copying itself. It simply separates into the two single chains. Then each chain serves as a model or a template against which the individual units of new chains line up in the right order. If the molecules come apart, the TANE chain picks up the units that make an ATEN chain, and the ATEN chain picks up the units that make a TANE chain, and you have two pairs. It's as if I started with paired hands, fingers tip-to-tip; took them apart; and imagined that the left hand were to make a right hand, and the right hand were to make a left hand from separate fingers. DNA and closely related molecules are the only ones known to science that can carry out this simple kind of replication.

How do these units know how to tell their complements? How does an A know that it must pick up a T? How does an N know that it must pick up an E? The separate units are floating around in a cell in which DNA molecules are replicating. When the N in the chain comes to an E, they will fit and stick together through specific hydrogen bonding. But if the N tries to pick up any of the other three units, N, A, or T, they will not fit and, therefore, not remain in place. One chain automatically picks up the units to make a new chain. These units are free in your cells right now. And your DNA molecules in some cells are coming apart and making new complements in this simple way.

THE TEST OF DNA REPLICATION

Do they really replicate in this way? It's a beautiful hypothesis, so beautiful that we're almost tempted to believe it without doing any testing. But nature has a way of fooling scientists. It often finds ways of working that scientists don't think of. So obviously it's important to test this hypothesis. One way is to label DNA molecules with stable isotopes. There are eight nitrogen atoms in a typical pair of units. The total molecular weight of the pair is about 700. If we were to substitute nitrogen-15 for the normal nitrogen-14 in one pair, the molecular weight would be increased by eight. Eight in 700 is about one per cent. This would not change the size of the molecule. Therefore, it would be more dense. Now if one could find a way to separate more dense molecules from less dense ones, it would be easy to test the hypothesis. As a matter of fact, three investigators, Mathew Meselson, Frank Stahl and Jerome Vinograd, a few years ago figured out a very simple way to do this. It is very much like the way a farmer separates wheat from chaff by shaking it up in a bucket of water. The chaff floats and the wheat settles and are, therefore, easily separated. You can do that with DNA molecules. You can separate heavy ones from light ones. It's a little more complicated than that. For one thing, it requires a $25,000 analytical ultracentrifuge instead of a bucket of water, but these days this is no problem because universities like The University of Michigan have them around.

With this method, it was possible for Meselson and Stahl to label the DNA units with nitrogen-15 and make them heavy, then to let them undergo one division in a medium in which only light nitrogen was present. The unit with heavy nitrogen comes apart and picks up light nitrogen. Of the two chains that start heavy, each will take a light partner. The new chains ought to be hybrid and intermediate in density. They are. In the next generation, the hybrid chain, the one with both heavy and light nitrogen, ought to separate into light and heavy chains. Each of these will pick up a light nitrogen partner. There will then be one hybrid chain and one completely light chain. And that, too, is found to be the case. In the next generation it is easy to figure out what happens. It does.

THE SYNTHESIS OF DNA

An even more dramatic way of testing the hypothesis was used by Arthur Kornberg and his associates, now at Stanford University. They set out to see if they could make DNA molecules copy themselves in a test tube. Everyone said it was impossible—that it was so elaborate a process that no biochemist could hope to make it happen in a test tube. Kornberg set out to do it and he found out, in fact, that it was quite simple. If you take the four DNA units with two extra phosphate groups on each, under the right conditions in a test tube, and drop in molecules of double DNA, the DNA will be replicated. It will make copies of itself. Single DNA chains are even more effective in the system. There are ways of telling that the copies are like the added primer.

Even more remarkable, one can make DNA molecules without having a model. One of these is a DNA that has A-T-A-T-A-T units in one chain and the complement in the other chain, T-A-T-A-T-A. If you use such an artificial DNA as a primer, it will be copied and the copy will be like the primer. Several of Kornberg's associates, using a somewhat different approach, discovered a way of making artificial double DNA molecules in which all the units in one chain are E and all the units in the other chain are N. They were then able to use this as a primer and show that in replication more molecules like the spontaneously formed $\frac{\text{N-N-N-N}}{\text{Ë-Ë-Ë-Ë}}$ are made.

All of this makes it difficult to believe that the hypothesis is incorrect.

THE TRANSLATION OF DNA

We now come to another interesting part of the story. How do we use a simple language like this—4 letters, 3-letter words, and only 64 words—to build an organism as complex as ourselves? It sounds fantastic. If you think a bit; you see it isn't. Any set of specifications that we can write in our 26-letter language can be written in a language with only 2 symbols, dots and dashes. As a matter of fact, computer language has only two symbols, and everyone knows that with it we can write any kind of information we want. It's true that in a computer you can't normally do it with such nice short words. These nice short three-letter words are what make the language of genetics so simple and elegant.

To know how we use this information to make us, we have to understand how we translate this language. Human beings are enormously complex, being made of many thousands of kinds of molecules. The DNA specifications have somehow to say, "Make all these molecules at the right time and in the right place and put them all together in the right way." To do this, one of the first steps is the translation of the four-letter language with its three-letter words into another kind of language, perhaps the second oldest living language on earth. It may have come into existence somewhat less than 3 billion years ago, that is, later than DNA. Of course, no one was around to say exactly when. So mine is only a rough guess. This language is called *Proteinese* because it is written in the form of protein molecules. These are long molecules somewhat like DNA molecules in being built of subunits. But there are 20 subunits in protein instead of 4 as in DNA. These subunits are amino acids. A typical amino acid has four or five kinds of atoms—carbon, hydrogen, oxygen, nitrogen, and, in some, sulfur. Note that they never contain phosphorus. These atoms are arranged in 20 specific ways to make the 20 units out of which we make proteins. We have some ten thousand, twenty thousand, perhaps a hundred thousand kinds of protein. These do many kinds of things. There are structural proteins. Hair is largely protein. So are fingernails. Hemoglobin, the pigment in red blood cells, is protein. All of the enzymes either are protein or contain protein. Enzymes speed up or catalyze almost all of the reactions that go on in a living system.

Let us now look at the characteristics of Proteinese as compared with DNAese. First of all, it differs in that there are 20 letters instead of 4. How about the words? The words in protein are not all of the same length. They can range from perhaps 100-letter words to 1,000-letter words. How many kinds of words can you write in protein? Remember, you can write only 64 in DNA. But using the information in the 64 words of DNA, you can write 20 kinds of words that, when used in a thousand-word message, will specify a protein a thousand units long. The first unit can be any one of 20, the second unit can be any one of 20. So it would be 20 times 20 times 20 a thousand times.

That is a number so large that for all practical purposes it is inconceivable. It is much, much larger than the total number of elementary atomic particles (electrons, protons, neutrons, and so forth) in the entire known universe. It is literally impossible to exhaust the number of combinations of words that you can make with 20 units, if they can be put together up to a thousand units long and in any proportion and in any sequence. This language, therefore, is essentially unlimited in the number of possible words.

PROTEIN SYNTHESIS

How do we make protein molecules with DNA units? This actually seems to be very simple. To do so we make use of another language, but fortunately it is only a dialect of the first one. How are the four letters of DNA translated into protein? If we write the four letters of DNA—N-E-A-T—we can write the complement of the DNA molecule in the dialect called RNA—ribonucleic acid. The complement of N will be an E which is almost like a DNA E. So we call it E′. E will have the complement, N′; A, the complement T′; T, the complement A′. Now, remember the letters form three-letter words. So, we have a word E′N′T′ that specifies an amino acid, say amino acid No. 1. We can have another word N′T′A′ that specifies amino acid No. 2.

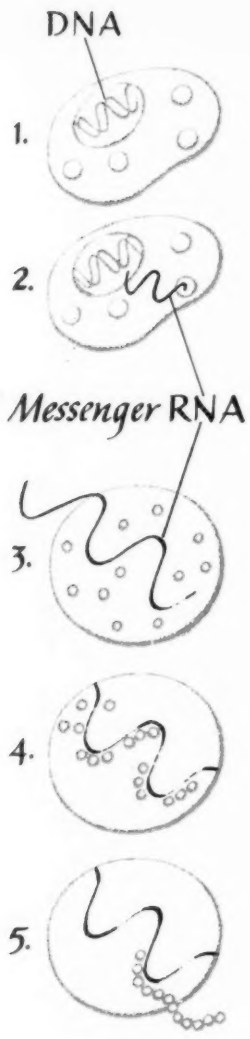
How is an amino acid related to a DNA word? It happens in the following way. The DNA code is in the nucleus of the cell. RNA that is complementary to this code is constructed. It moves from the nucleus to the cytoplasm and there enters small microscopic structures called ribosomes. This information-carrying RNA that specifies a protein goes into the ribosome and there serves as a template to collect amino acids in the right sequence. Each of the 20 amino acids is tagged with a small segment of RNA, called transfer RNA, consisting of about 80 units. There are 20 transfer RNA's, corresponding to the 20 amino acids. Each carries a three-letter coding segment complementary to a three-letter coding segment on the template RNA. An enzymatically catalyzed reaction joins the amino acids together to form a protein molecule. This then leaves the ribosome. This is the way we make hemoglobin. You are doing this right now in your red blood cells. Interestingly enough, this process of translating the information from DNA to RNA can be done in a test tube. And the process of transferring the information from RNA to protein can also be carried out in a test tube. It is now possible to make test tube hemoglobin by following these steps. This makes it pretty clear that this is the right interpretation. That all this can be accomplished in a test tube is a remarkable achievement of modern molecular biology.

ENZYMES

For what are proteins used? Let's take the protein that catalyzes the reaction by which the amino acid phenylalanine is oxidized. One oxygen atom, added in a particular place, makes the related amino acid tyrosine. We must have both of these amino acids. If we have an enzyme that says we can make tyrosine from phenylalanine, we don't have to have tyrosine in our diets. We can make the tyrosine by this reaction which is catalyzed by an enzyme which was made from a piece of DNA which we call a gene. Some people have a defective form of this enzyme and cannot catalyze the reaction by which tyrosine is made from phenylalanine. If such persons are fed normal amounts of phenylalanine, as in a usual diet, they cannot convert the phenylalanine into tyrosine. They use some of the phenylalanine for protein but the rest of it, the surplus, accumulates and indirectly poisons the central nervous system. Such individuals are feebleminded. This genetic disease is called phenylketonuria, and in English one describes it as feeblemindedness due to inability to oxidize phenylalanine to tyrosine because of the absence of a protein. The gene that says the same thing in DNAese says so in a "sentence" of perhaps 500 or a thousand "words."

GENETIC DISEASE

We know of several hundred genetic diseases in man. Phenylketonuria is an interesting one. If diagnosed early, which is simple, and if an artificial diet is provided in which there is only enough phenylalanine to make protein and no excess, and if tyrosine is provided in the right amount, the individual becomes normal. The result is circumvention of a genetic disease by modern medicine. But note that this is accomplished without correcting the fundamental defect in the specifications. Such



From DNA to Protein:

1. The DNA chain in the nucleus of the cell specifies a complementary messenger RNA chain.
2. The messenger RNA leaves the nucleus.
3. The messenger RNA reaches the ribosomes.
4. The RNA specifies the sequence of amino acids.
5. The amino acids are joined to form a specific protein and leave the ribosomes.

The protein can remain in the cell or move out of the cell to perform a function elsewhere in the body.

a "cured" individual will transmit defective specifications to the next generation. This creates a eugenic problem that someday society may have to be concerned about. It isn't quite as bad as it sounds because the buildup of this defect as a result of this achievement of medical science is very slow indeed. It would take many, many generations and many thousands of years before this particular disease would become frequent. On the other hand, there may someday be many genetic diseases similarly circumvented. If so, we will sooner or later have to think about what to do about them. I point out, however, that this isn't a question for science alone. It is a question for society, including scientists. One solution is simple. Persons who are of this type might be persuaded to adopt children instead of having them in a natural way. There would then be no buildup. But as I say, it is not a scientific question, and I am no more competent to advise than is any other informed citizen.

CYTOPLASM

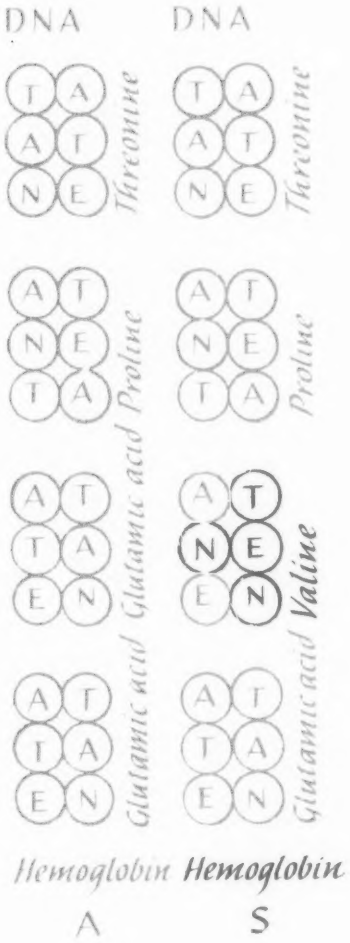
I am sure many of you are saying life can't be this simple. Of course it isn't. We have DNA specifications in the nucleus of the cell that are, so to speak, the blueprints or the recipes for making people out of egg cells. But a lot more is essential, too. In addition to these specifications, the egg also contains cytoplasm. And that, too, is specific. It must be human cytoplasm. You can't put the nucleus of a human egg into the cytoplasm of a monkey egg and get an organism. It won't work. Of course we don't do this experiment with monkeys and people, but we can do it with two kinds of frogs. We can find that the nucleus has to be in its own species of cytoplasm. Therefore, the cytoplasm is species-specific. We don't know too much about this as yet. We must leave some problems for the Ph. D. candidates of the next generation.

In addition to cytoplasm, one must have food—raw materials—to make an organism as complex as one of us from an egg cell, given the proper specifications. This food must be of the right kind, in the right amount, in the right proportions, and available at the right time. If these conditions are not all fulfilled, the result is nutritional disease. Each of us has consumed 10, 20, or 30 tons of food up to now, depending on age and appetite. We have used that food to make us, using a set of speci-

fications, tearing it down with enzymes, using the pieces to construct one of us. If the specifications aren't right, or if the raw material isn't right, the individual doesn't come out right.

MUTATION

Let us now turn to the last question. How do differences arise? Why am I different from other people? I have different specifications, but how did they come to be different? The answer is pretty simple. Sometimes DNA molecules make a mistake in being copied. An N unit doesn't always pick up an E unit because the hydrogen atoms that must be in the right place to make them stick together by hydrogen bonding have a way of being in alternate positions occasionally. If the hydrogen atoms happen to be in the wrong place exactly when the molecule is going to pick up its partner, the N may pick up an A instead of an E. Let's say that we have a three-letter word, TEN. The complement to that would be ANE. Now let's say that the E picks up a T instead of what it should pick up, an N. Then the complement would be ATE. Now when this ATE replicates in the next round, it is not likely to make a mistake. The complement of ATE is TAN. By substituting an A for an E, we have now substituted the word TAN for the word TEN. That is what we call a mutation. TAN will not stand for the same amino acid as does TEN. If this change occurs in the message, there will be a wrong amino acid in the protein at a particular place. This type of change is known to happen. For example, there are forms of hemoglobin that differ by one amino acid. Sicklecell hemoglobin, which is an unfavorable kind of hemoglobin to have, differs by one amino acid at a particular place because one symbol in the DNA code was miscopied at some time in the past. This is not the only way a mutation can occur. A letter can be left out, an extra one inserted, or letters can be transposed. Or these can be more complex changes like those that occur in typewriting when one gets a hand on the wrong row of keys. Sometimes an entire "chapter" may be present as an "extra." Thus in mongolian idiocy there is present in each cell an entire extra chromosome.



A hypothetical version of how a change in one letter in a DNA message can produce a mutation that alters the sequence of amino acids, resulting in a different protein. The left-hand column represents the formation of a segment of a normal hemoglobin A, containing 150 amino acids.
The right-hand column represents sicklecell hemoglobin, which differs from hemoglobin A in that valine replaces one unit of glutamic acid. This difference was caused by a change in only one DNA letter in the hemoglobin gene.

BREAKING THE CODE

How do we know that the DNA words designating amino acids are three-letter words? How do scientists go about discovering this? How do we know what order of the DNA unit stands for what amino acid? That is, what is the coding relation between DNA and protein? This is like trying to decipher any code. What you do is find the equivalent of a Rosetta stone on which you have both messages written. Then, you can find out how one is related to the other. We have, so to speak, found the Rosetta stone of life that relates DNA to protein. This was done in a most interesting way. Prof. Severo Ochoa at New York University found that he could make RNA molecules artificially by putting the RNA units together in a test tube under the right conditions. If you put in all A′ units, you will get an RNA that has only A′ in it. If you put in all T′, you will get RNA made only of T′. If you put in T′ and A′, you will get an RNA that has T′ and A′. If the T′ and A′ are in equal proportions, they will go together at random in equal proportions. If you put in all four DNA units, T′A′N′E′, they too will go together at random.

A few years ago Marshall W. Nirenberg and J. Heinrich Matthaei of the National Institutes of Health thought of putting into the test tube system, in which they did the translation of RNA to protein, artificial RNA. When they used an artificial RNA containing only T′ units, lo and behold, it did direct synthesis of a very peculiar and previously unknown protein—namely, a protein made of only the one amino acid phenylalanine. This is not really a protein but a protein-like polymer called polyphenylalanine. This was a clue to breaking the code. The units had to make sense or they couldn't have made that particular protein. Whatever the coding ratio is, whether it is two-letter words, three-letter words, four-letter words, the amino acid is always the same—phenylalanine. This told Nirenberg and Matthaei that if the words are indeed three-letter words, the coding word for the amino acid phenylalanine must be T′T′T′.[2]

Now you can make a synthetic RNA in which you have T′ and A′. If you put in a ratio of five times as many T′ as A′ and get a random association, it is easy to calculate the relative frequencies of the various possible three-letter words. Words with two T′s and one A′ will be relatively frequent. So will T′T′T′ words. It turns out that two of the amino acids that are incorporated in the protein when this experiment is made are phenylalanine and tyrosine. The coding word for tyrosine is therefore probably two T′s and an A′. But there are three possible ways to arrange the word. You can put the A′ first, second, or last. How do you know which way is the right way? That turns out to be simple too. Professor Ochoa found that if he started out with the one letter A′, and then built up an RNA using all T′s for the remaining units he got an RNA that had an A′ at the end and all the rest T′s, that is, . . . T′T′T′T′T′T′T′A′. RNA gets synthesized from right to left; the protein gets built against it from left to right. We know this from radioactive tracers. When Ochoa used this RNA, he got a protein containing, for the most part, phenylalanine, as he should. Remember three T′s equal phenylalanine. But, there was a small amount of tyrosine incorporated. It was always at the final end of the chain to be made. Obviously, if tyrosine is two T′s and an A′, it has to be in the arrangement, T′T′A′. By doing other experiments of this kind, it is possible to work out other code words. This is what workers have done and are doing. As a result, we know code words for 19 of the amino acids. If you know the order of the amino acids in a protein, such as Frederick Sanger worked out for insulin, you can now come pretty close to reading the DNA message that spelled the amino acid sequence in the protein. I've simplified the story considerably, but that is approximately where we are now.

It turns out that there are 64 words possible in DNAese, and it only takes 20 to encode the 20 amino acids. What are the other 44 doing? For one thing, there is pretty clearly some degeneracy in the code. That means there are two or more words that encode the same amino acid. Then too, some of the words are probably used as spacers, to indicate where one protein stops and another begins. Perhaps one tells where to start reading the message. With no spaces, there must be a fixed starting point for reading the message. This kind of code is called a nonoverlapping code because the letters must be read three at a time starting at a

[2] The usual symbols for DNA nucleotides are A, T, C, and G. For RNA A, U, C, and G, I've used the ones I have so as to be able to make twenty 3-letter English words.

predetermined point. And it is a degenerate code, because one word might stand for the same amino acid as does another word.

THREE-LETTER WORDS

Now we've answered all the questions except one How do we know that the words in this language are three-letter words? That turns out to be very simple too. And it's done this way. I have a message ANNNANATETANANTANTATETNTNAEANT, which makes some sense in terms of our own language. It says ANN NAN ATE TAN ANT, etc. Crick and some of his associates took a DNA message like this that they knew made sense. Then they made mutations near the left end by adding or subtracting units. If they took one letter out, the message no longer made sense. If I take the first letter away from the example given, it now reads NNN ANA TET, etc. Taking one letter out shifted the reading frame by one and scrambled the message. If you take out one letter and then put in another letter, the one you put in will compensate for the one you took out, and the message will make sense at one end; e.g., TNN NAN ATE TAN ANT, etc. If you take out two letters, the message won't make sense; e.g., NNA NAT ETA, etc. But, if you take out three letters, most of the message will make sense; e.g., NAN ATE TAN ANT, etc. Or if you put three in the left end, the right end will retain its sense. But if you take out two or put in two, take out one or put in one, take out four or put in four, the message will not make sense. The only simple way to explain such results is to assume that the language consists of three-letter words.

EVOLUTION

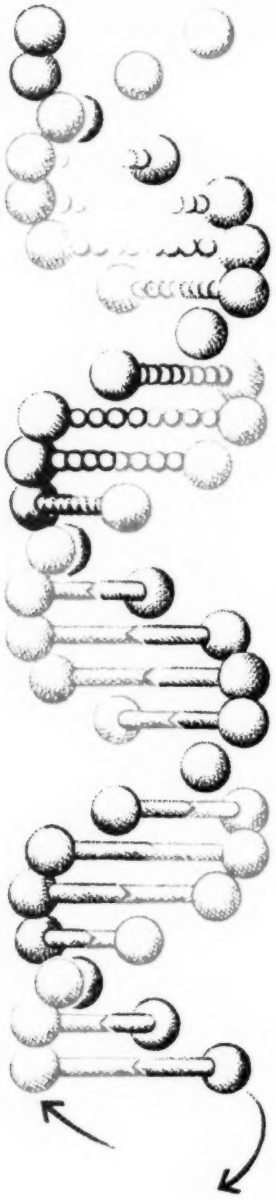
Let us now talk about evolution. These changes—taking out letters, putting them in, and rearranging them—are believed to be the basis of all organic evolution from the beginning of life on earth to the origin of man. We are of course the product of evolution and the result of many, many millions of mutations which had selective advantages. These mutations have given rise to an evolutionary sequence going back from us, if you call man the ultimate form of evolution at the present time, to simpler and simpler forms to something akin to the simplest viruses. Instead of the 5 billion units in the DNA of humans, the smallest viruses have only a few thousand units of DNA or RNA in their genetic specifications.

Before viruses, it is presumed that there arose spontaneously on earth in the prelife stages, DNA or RNA molecules that were able to copy themselves. Some presumably collected protein coats that provided protection. This gave them a selective advantage. The units, out of which DNA was made, presumably came from simpler organic molecules by chemical reactions which are inevitable under favorable conditions. They, in turn, came from simpler molecules that were inorganic. These, in turn, came from the elements. We now know that all the elements are capable of coming from hydrogen by nuclear interactions that nuclear physicists know about. Hydrogen fuses to give helium, helium fuses to give beryllium 8, beryllium 8 captures helium nuclei and becomes carbon. And so it goes. All of this is known in principle now. If this is correct, it means that from the first postulated primitive universe of hydrogen all of evolution is possible up to man.

That sounds very mechanistic, I know. At this point, I should say it really isn't any more remarkable that there should have been created a universe of hydrogen capable of evolving into man than that there should have been created a universe already containing man. One course is as remarkable as the other. In other words, the hypothesis I have advanced does not change the problem of ultimate creation one iota. In that sense, it has nothing to do with religion, which is an entirely separate matter.

CULTURAL INHERITANCE

As far as we know, we differ from all other organisms on earth in a *quantitative* way only. Maybe there is something we do not yet know that makes us qualitatively different from other organisms. If so, we do not know what it is. Quantitatively, however, we have a great deal that other organisms do not have. For one thing, we have a more highly developed nervous system than any other organism on earth. As a result, we have better memories. We are able to reason. Maybe other animals can reason too, but we are much better at it, there is no doubt about that. We have been able to develop a method of communication by speech. Other organisms have primitive ways of communicating by



sound, but they do not have speech in the sense in which we have it. We have learned to write down messages that are equivalent to DNA. We have developed through speech and writing very effective methods of communication. These methods of communication and the ability to reason, to store information in our nervous systems, to take it out, to rearrange it, and to communicate it, make possible the evolution of a cultural inheritance which we alone among all creatures on earth possess. This inheritance includes language, religion, music, literature, art, technology, and science.

No other organism has added this type of cultural inheritance to its biological inheritance. We accumulate our cultural inheritance individually; we transmit it to our fellow man, and we transmit it to the next generation in a cumulative fashion. Our educational institutions are engaged in the process of systematically transmitting such information to the next generation and in adding to it in a cumulative way from one generation to the next. This is in addition to and separate from our biological inheritance in its manner of accumulation, storage and transmission. As a matter of fact, we don't know how the information that we accumulate is stored in our nervous systems. This again is a problem for the next generation, and a very important one. Although we do not know how this is done, we do know that cultural inheritance cannot develop without biological inheritance through DNA—for we know our brains are made according to the specifications in DNA. The two types of inheritance are complementary.

The assumed evolutionary sequence from hydrogen to man has proceeded through a fantastic number of steps, each almost imperceptibly small. Each represents a chemical change such as the fusion of hydrogen to form helium or the modification of a DNA "letter" by a simple chemical reaction. Through science, which is a part of our cultural inheritance, we have identified many of these evolutionary steps. The humanities, too, are a part of our cultural inheritance. In this sense, the two areas are closely related. If we are to understand and appreciate our total cultural inheritance, as we believe liberally educated men and women should, we cannot reasonably disregard any of its major components.

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National Referral Center for Science, Technology: A Progress Report

THE National Referral Center for Science and Technology, established with the support of the National Science Foundation in the Library of Congress, marks its first year of service to the scientific and technical community.

Designed as a clearinghouse to make information resources known to the country's scientists and engineers and to assure the fullest possible use of these resources, the National Referral Center has four major responsibilities: (1) identifying all significant information resources in science and technology, (2) acquiring, cataloging, and correlating substantive and procedural data about the nature, scope, and capabilities of these resources, (3) providing advice and guidance about these resources to any organization or individual by replying to requests and by publishing directories and guides in selected subject fields, and (4) exploring the roles and relationships that exist or should exist among the many elements of the scientific and technical information complex.

More than 8,500 potential information resources have been identified and this number is growing steadily at the rate of more than 100 each week. The data being collected pertain to special libraries, information and documentation centers, abstracting, indexing, and translating services, experiment stations, observatories, research laboratories, museums, and other organizations and facilities.

For each resource, the Center is establishing a detailed record that describes the subject specialization, language coverage, kinds of material acquired, and how this material is processed. All these records will be regularly updated. The Center also determines what services are provided—such as answers to technical questions, literature searches, data compilations, and consultations—and the conditions or restrictions that control the use of these services.

According to its latest progress report, the Center had logged more than 1,500 requests for identification of information resources. Although this total is not high, the varied origins of these requests and the tremendous variety of subjects they cover are encouraging evidence of the need for the central switching mechanism the Center represents.

About 50 percent of the requests have come from industry and commerce, 14 percent from academic research and nonprofit organizations, 18 percent from government activities, and the remainder from individuals.

In addition to answering requests, the Referral Center has begun preparation of its first directory. Scheduled for publication this year, the directory will consist of three volumes listing major scientific information activities. Two volumes, one covering the physical sciences and the other biological sciences, will be prepared by the Center. A third volume will be the product of a survey of information resources in the social sciences that is being conducted by the Bureau of Applied Research, Columbia University.

The Center emphasizes that it does not store, process, or disseminate scientific literature. Nor does it provide direct and specific answers to technical questions or furnish bibliographic assistance. Instead, its objective is to serve as an intermediary between the technical community and the Nation's vast informaion resources.

Estrous Cycle Control in Domestic Animals

A Conference Report

On July 9–10, the Cooperative State Research Service and the Agricultural Research Service, U.S. Department of Agriculture, in cooperation with the University of Nebraska, sponsored a 2-day conference designed to evaluate methods for controlling the estrous cycle in domestic animals. The conference was held at the Nebraska Center for Continuing Education, University of Nebraska, Lincoln.

Through formal papers and general discussion, conference participants reviewed major problem areas and discussed the pressing needs for further research, in addition to evaluating present control methods.

Review presents here one of the formal papers of the conference, together with summaries of those papers which were available at press time.

The complete proceedings of the conference, including the discussions and formal summary, will be published by the Department of Agriculture at an early date.

MODIFYING THE NATURAL ESTRUAL RHYTHM: Side-Effects and After-Effects of Experimental Endocrine Treatments

L. E. Casida

The side-effects and after-effects considered in this discussion are those which grow out of experimental attempts to modify the natural estrual rhythm, and which have a bearing on the subsequent fertility of the animal They are the effects that are both the despair and the hope of workers on technological control of reproduction. They are the despair in that they detract from our immediate ability to control reproduction; they are the hope in that we may be able to learn more about the reproductive process in our attempts to analyze and understand them.

At least four ways have been suggested for altering or controlling the estrual cycle and the consequent breeding time in livestock.

1. The induction of ovulation and the initiation of pregnancy as the direct result of treatment with gonadotropic hormones.
2. Induction of new corpora lutea in all animals of the herd at the same time by injection of gonadotropins. The estrual cycle in the different animals then taking as its time of departure the formation of the new corpora lutea, and all animals coming back into estrus at the same time.
3. Inhibition of ovulation in the different animals of the herd, simultaneously, for such a minimal period of time as is necessary for the ovaries of all animals to become free of functional luteal tissue—cessation of the inhibitory treatment then being followed by estrus in all animals at approximately the same time.
4. Destruction of the corpora lutea in the different animals at the same time, no matter what the stage of their development with the consequent return of all animals into estrus at the same time.

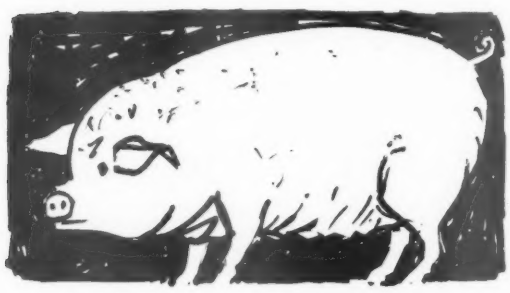
The first of these presumes that ovulation and fertility can be brought about regardless of the state of the estrual cycle at the time of treatment.

The second of these assumes that the new corpora lutea take command of the cycle and that the old corpora lutea either regress at their initially appointed time or that they continue on and then regress at the time of the new corpora lutea, presumably one estrual cycle length from the time of the induction of ovulation. It is hoped, of course, that the different animals will respond very much alike to this treatment so that the date at which they come back into estrus after regression of the newly formed corpora lutea will show much less variation than the initially anticipated time of estrus.

The third suggested method implies the application of the treatment at different stages of the cycle and inhibition of estrus for different lengths of time in the different animals. In general, those animals in which treatment is initiated early in the cycle will be held out of the anticipated estrus the shortest time. Those later in the cycle will be held out for a longer time. There is a stage late enough, however, that there is no interference with the next estrus and treatment will have ceased before the following one. It is presumed again that the interruptions and modifications of the normal physiology will leave no imbalance resulting in aberrations leading to lowered fertility.

In the fourth instance, instead of the cycle being lengthened as in the third, it is being shortened by destruction of the corpora lutea. It is the hope that the method of destroying the corpora lutea will not be generally harmful to the health of the individual nor lessen the fertility of the return estrus.

For all of the four suggested methods of altering the estrual cycle and controlling the breeding time, there are good theoretical reasons for expecting them to work. The danger, however, is that unanticipated side-effects or after-effects, not necessarily injurious to the animal's health, may affect the immediate or the subsequent fertility of the animal.



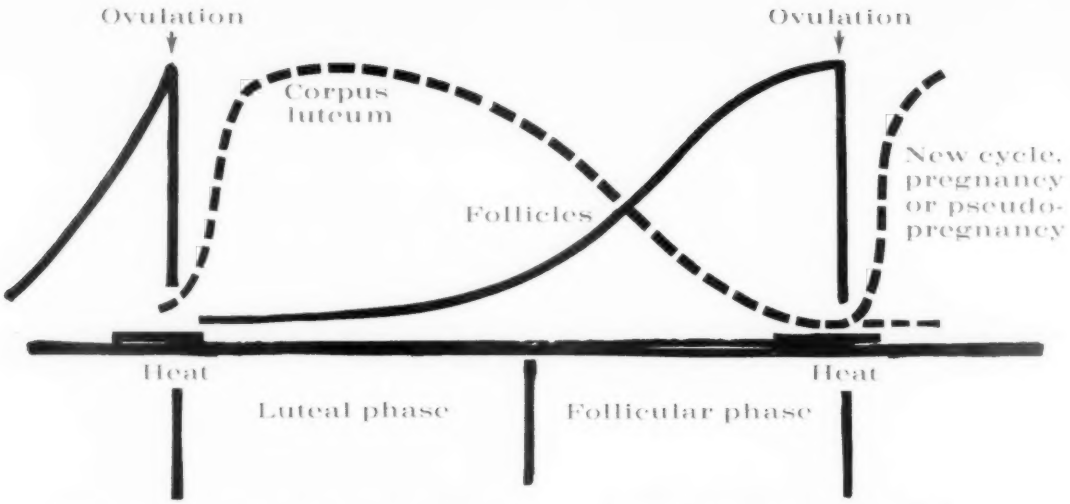
It was early shown in cattle (*8*)[1] that ovulation can be induced at most any stage of the estrual cycle and during the post partum interval. However, in many of these individuals, insemination did not lead to pregnancy. In fact it did not lead to fertility of the eggs except as ovulation was brought about during the follicular phase of the cycle very near to the time of expected estrus. Similar results were demonstrated in the sheep (*18*) and also in the rabbit (*19*). In general, eggs that were ovulated during the follicular phase of the cycle were fertilizable and those during the luteal phase were not fertilizable.

Further studies with the rabbit (*17*) indicated that eggs ovulated during the luteal phase of the cycle could be fertilized if the semen were introduced directly into the uterus rather than being deposited into the vagina. Similar attempts in the cow (*6*) and in the pig (*26*) also showed fertility for the luteal-phase eggs, but in general the fertilization rate was low and in all three species the uterine insemination in the luteal phase of the cycle quite commonly led to the development of pyometra (*6*). The condition was explored further in the rabbit (*3*) and although fertilization could be accomplished, embryo survival was particularly low, presumably because of the pyometra that had been induced by insemination. This was believed so because if the young embryos were removed from the oviducts of the luteal phase animals and were transplanted into oviducts of other luteal phase animals that had not been inseminated, the embryos survived.

It was shown also in the rabbit (*4*) that administration of progesterone to the follicular-phase animal effected a marked depression in the fertilization rate. The explanation of this depressing effect of progesterone may lie partly in the poor transport of sperm and possibly in poor capacitation of the sperm.

When new corpora lutea are induced in all animals of the herd at the same time, it is hoped that

[1] Italic numbers in parentheses refer to "Literature Cited," p. 19.

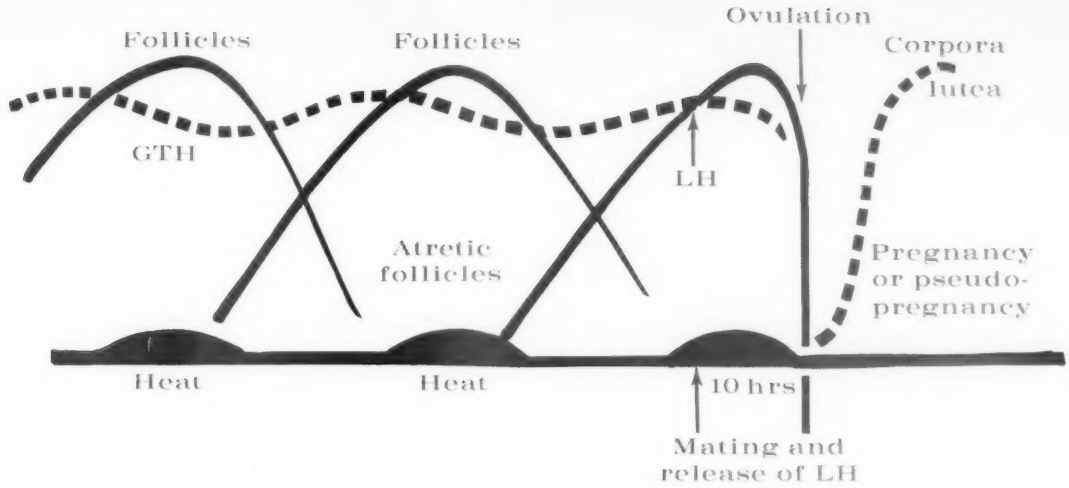


the interval to next estrus may be more uniformly related to the time of the formation of the new corpora lutea than to the time of the preceding estrus. Attempts to regularize the interval to next estrus in sheep by the injection of gonadotropic hormones at different stages of the estrual cycle (*7*) have given different results depending upon the time at which the sheep were injected and depending upon the kind of gonadotropic preparation. Initial studies were made by subcutaneous injection with a purified follicle-stimulating extract to increase the number of ovulable follicles, and following this by intravenous injection of an unfractionated mixture of FSH and LH. Other sheep were injected subcutaneously with unfractionated extracts to grow a larger number of follicles and followed then by an intravenous injection of the same preparation to produce ovulation. Subcutaneous treatment with unfractionated extracts increased the intervals to the next estrus to an average of 25 to 31 days depending on whether the treatment terminated on the 9th or the 13th days of the estrual cycle.

The variation in length of cycle was increased tremendously, so that in no sense was there a regularization of the interval, nor was there a timing of next estrus to a normal cycle length from the time of induced ovulation. When the number of follicles that responded had been increased by giving FSH rather than unfractionated extract, the results differed according to the stage at which the treatment was given. The time of the next estrus and the variability in the time that the next estrus occurred were virtually unaffected when treatment terminated on the 9th day of the estrual cycle, but estrus was delayed on the average and the variability was increased greatly when treatment terminated on the 13th day.

The delay in the next estrus and the variability in the time of next estrus were probably traceable to the formation of a number of cystic follicles and luteinized cysts. These were more prevalent with the unfractionated extract than with the follicle-stimulating preparation. With both preparations, however, there were instances of anestrual intervals of more than 60–70 days with one ovary still containing more than 10 functional-appearing corpora lutea and the other ovary only regressed corpora lutea. There may have been recurrent superovulation after treatment in these cases or there may have been persistence of corpora lutea on a local basis for an unusual length of time.

There is also the work with sheep (*13*) where ovulation was induced by injection of fairly minimal amounts of HCG or of unfractionated extracts of the pituitary gland. In these cases, the induction of new corpora lutea at different stages of the cycle with a minimum of follicle stimulation has had no effect on the interval to the next estrus. The mere induction of ovulation does not appear to disturb the rhythm of the estrual cycle, but if superovulation is induced as in the earlier studies there may be a sequence of events which leads to the formation of accessory corpora lutea, follicular cysts, and luteinized follicular cysts—all of which tend to delay the next estrus for a variable length of time.



There is an apparent difference between sheep and swine in the response to minimal amounts of HCG. Species-normal numbers of new corpora lutea or fewer have been induced in gilts at 5, 10, or 15 days of the cycle (*23*) and these glands have persisted and prevented estrus in most instances until slaughter on day 24. Insufficient data are available from any source on the uniformity of the length of the interval until the next estrus. The prospect is complicated by a considerable proportion of animals showing delayed formations of accessory corpora lutea following this treatment.

The initial study of the inhibition of ovulation in farm animals by administration of progesterone (*9*) demonstrated many aspects of our present knowledge of the effects of this treatment. Suboptimal dosage showed a tendency to permit ovulation during the course of treatment. There was also a greater incidence of cystic follicles at the end of treatment than with a more optimal dosage. The time of recurrence of estrus was earlier, and in general the fertility level was lower when the suboptimal dosage was used. Later and more complete analysis of dosage effects (*10*) has shown that the lowest levels fail to inhibit estrus and ovulation. At a higher level there is inhibition of estrus and ovulation with the formation of cystic follicles during treatment. At a still higher level, there is inhibition of follicular development, estrus, and ovulation during treatment with a uniform posttreatment estrus and ovulation. At the highest levels there is an extreme inhibition of follicular development during treatment with a marked delay or an absence of estrus following treatment. During the delay interval there is a strong tendency for cystic follicles to develop.

Species differences appear to exist in the efficacy with which progesterone may be used to control the occurrence of estrus in a group of animals. The initial study on synchronization of lambing and shortening of the lambing interval (*20*) gave results that were quite clear cut and there was no lessening of fertility. Other studies (*27*) with sheep and to a certain extent with cattle, particularly when progesterone was injected, have borne out much of the original promise. In general, the degree of synchronization in swine and the fertility level have been lower than with the ruminants, particularly sheep.

Evidence as to how progesterone administration may affect fertility in swine (*1*) is indicated by an increased percentage of eggs lost as measured by the discrepancy between number of corpora lutea and number of recovered ova. Also, there was a greater percentage of unfertilized eggs, but embryonic death did not appear to be increased.

That high dosages of progesterone may have a latent effect on the pituitary-ovarian relationship (*14*) was demonstrated in the lack of change in pituitary gonadotropin content during the posttreatment period despite the fact that follicular development was increasing steadily with cyst production. This is in contrast to the decline in pituitary gonadotropin (*11*) concomitant with the resumption of normal ovarian activity in the period following a modest course of treatment with progesterone injections.

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A clinical practice in treating cows showing absence of estrus is the manual removal of the corpus luteum from the ovaries by way of the rectum. Estrus often occurs within a few days after this removal. This is about the only technique available at the present time for effecting the destruction of corpora lutea in different animals at the same time. Removal of the corpora lutea in the ewe (*13*) at days 5, 9, or 13 leads to return of estrus in 2 to 3½ days. Estrus recurs after 2 to 6 days in most normal cows when corpora are removed at days 7–17 of the cycle (unpublished data, University of Wisconsin). Limited data (*23*) for the pig suggest a slightly longer interval before estrus resumes. Another possible approach to destruction of the corpus luteum (*28, 24, 16*) is to interfere with its formation so that it may be maintained for a shorter than normal time. There is evidence that administration of progesterone to the sheep, pig, and cow in the early part of the cycle results in smaller and less well developed glands. There seem to be little data, however, as to whether such corpora have shorter than normal life.

The likelihood of the animal developing cystic ovaries following the heat after removal of the corpus luteum appears to be somewhat enhanced (unpublished data, University of Wisconsin). This likelihood may be increased even further if two or more corpora lutea are removed in succession (*12*). A similar phenomenon was shown also (*5*) in swine from which part of the corpora lutea were removed by unilateral ovariectomy; the incidence of cystic ovaries was increased.

Another experimental modification of the normal reproductive cycle which probably increases the chances of cyst formation is the removal of pigs at birth. Baker *et al.* (*2*) showed a rather unusual incidence of cystic ovaries in animals so treated, as did Self and Grummer (*22*) when litters were weaned at 10 days of age. More recent data (*21*) have shown a higher incidence of cystic ovaries in sows from which the pigs were removed at birth than in those from which pigs were removed at 21 days.

Various treatments in which suppression of ovarian activity has been removed suddenly, whether it be by withdrawal of heavy doses of progesterone or by removal of corpora lutea or by parturition without the inhibitory followup of nursing, have resulted in increased probability of ovarian disfunction.

Finally, consideration will be given to certain experimental situations which seem characterized by low fertilization rates. It was shown in sheep (*18*) that ovulation could be induced during anestrus by injecting gonadotropic hormones. Estrus did not occur in these animals, but the fertilization occurence was virtually nil when artificial insemination was performed near the time of ovulation.

Another illustration has been shown in beef cattle (*15*) where ovulation has been induced rather regularly by injection of gonadotropic hormone approximately 2 weeks after calving. The fertility of these eggs following artificial insemination also appears to be nil. A similar low fertilization rate of eggs from sows treated with gonadotropins shortly after parturition (*21*) has also been demonstrated. Making eggs available for fertilization without the occurrence of estrus has not led to appreciable fertility with the exception noted earlier at the time of the luteal phase of the cycle when fertilization might be produced by insemination into the uterus. In that instance, however, the best results have been obtained in the rabbit where the intravenous injection of the gonadotropin causes regression of the corpus luteum with a presumed quick decline in progesterone (*25*).

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ROLES OF HYPOTHALAMUS AND HYPOPHYSIS IN ESTROUS CYCLE CONTROL

The phenomena which clearly involve participation of the hypothalamus in hypophysial control of reproductive function, in my opinion, have not been given the attention they deserve by American reproductive physiologists. I shall omit the details of the fascinating studies on rats and mice performed by Whitten and by Bruce which showed that odor of males is capable of profoundly modifying the reproductive behavior of females. The Whitten effect demonstrates that presence of males can in fact synchronize time of ovulation in a group of females by hastening or delaying heat and ovulation in a significant number of members of a mouse population. The Bruce effect is equally fascinating in that it shows that male odor can interrupt a previously initiated pregnancy at the early blastocyst stage by causing the cessation of release of hypophysial prolactin, the LTH of mice.

Some years ago we were greatly puzzled by the fact that pigs which did not settle to repeated services on their home farms, and which were sold as being sterile to research workers at the University of Illinois, conceived at the first service after being shipped by truck to the new location. Our data showed that about 50 percent of the hogs sold as "sterile" had no anatomical or endocrine abnormalities (Wilson et al.)[1] Infections, male sterility, or nutritional deficiences having been largely ruled out as the possible causes of "sterility," the truck ride was the only event that intervened between "sterility" and sudden fertility. The reason for this marked change in fertility level remains unknown. Similarly puzzling is the observation made by several independent workers, but not adequately documented in the literature, that a significant amount of synchronization of sexual activity occurs in normal gilts if they are shipped from one place to another. About 5 to 7 days after arrival at the new place of habitation, a significantly greater number of shipped females show heat than would be expected to do so on a random basis.

In one experiment (Du Mesnil du Buisson *et al.*)[2] 45 percent or 465 prepubertal females, showed heat 1 to 9 days after being shipped, while only 180 females should have been in heat during this period had the random nature of this phenomenon not been disrupted by shipping. In addition to the effect of synchronization, the same experiment also indicates that the onset of sexual maturity was hastened either by the stress of transportation, or by the new environment, or by the daily checking of the females for heat by males.

The French group of workers has other studies which implicate the hypothalamo-hypophysial axis as a mediator in the modification of reproductive responses.

Domestic mammals show a variant of the long-known lordosis reflex of small laboratory mammals which has been analyzed in pigs by Signoret.[3] He has confirmed the observations of many practical pig breeders that a sow in heat will become rigidly immobile when, in the absence of a boar, a man sits on her or even simply exerts manual pressure on the back. The degree to which this response can be obtained appears to be genetically controlled. Signoret noted that the proportion of females responding could be greatly increased if a male was present, and he proceeded to fractionate the role of the male in eliciting the reflex. He found that both the odor of the male and a recording of his typical rutting call raised the response of the female.

How the phenomena of sound and odor can intensify psychological heat, which is normally attributed to the action of estrogen on the central nervous system, remains completely unknown and invites further study. Of great interest is the fact that there is a very significant relationship between the readiness with which the rigidity reflex can be induced and the fertility of swine.

Olfaction in pigs, in addition to being related in some way to the intensification of the psychological heat response, is perhaps implicated in LH release. Signoret and Mauleon [4] removed the olfactory bulbs from pigs and found that their cycles became irregular or ceased completely. The corpora lutea in the ovaries of these females disappeared, and

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there was an increase in the number of vesicular follicles which were about half as large as those of ovulatory size. These observations suggest the possibility that absence of olfactory bulbs does not interfere with FSH secretion, but seems to prevent LH release either *in toto* or at least in sufficient quantities to cause the ovulatory spurt and ovulation. The morphology of these ovaries is reminiscent of the ovaries of rats in constant estrus which can be produced either by continuous lighting or hypothalamic lesions or by the single treatment of prepubertal rats with steroid hormones. In all of these cases the continuous follicular condition of the ovaries is known to be caused by a derangement of the LH storage or release mechanisms, or both.

Some aspects of neuroendocrinology remain, in my opinion, inadequately explored by those of us working with reproductive physiology of domestic animals. The involvement of the hypothalamus in the control of pituitary function can no longer be doubted. Some of the data reviewed strongly support the possibility that many environmental factors (odor, crowding, excitement, etc.) play an important role in significantly modifying the endocrine relationships between the hypothalamus-hypophysial axis and the endorgans. It seems important to start intensive investigation of the degree to which the exteroceptive factors do modify the endocrine stability of domestic animals, especially insofar as reproductive phenomena are concerned. It appears equally important to initiate research on the possible use of hypothalamic releasing factors in the control of physiological function of animals other than the laboratory rat.

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EVALUATION OF METHODS FOR CONTROLLING THE ESTROUS CYCLE

Truly effective estrous cycle synchronization techniques are of great potential value to commercial producers of beef and dairy cattle, sheep, and swine. Many commercial beef-cattle men recognize the merits of using outstanding sires through artificial insemination (AI) to produce greater numbers of faster gaining cattle having the most desirable carcass characteristics. The relatively high heritability of feedlot gains makes this idea particularly attractive. Nevertheless, progress in attaining this goal has been rather slow, mainly because of the practical problems involved in breeding range cattle artificially and the low conception rates frequently obtained. Methods for cycle regulation compatible with the most commonly used management practices can play a major role in facilitating the widespread use of artificial insemination and improved selection techniques to the beef industry.

The major application of estrous cycle regulation techniques in dairy cattle is in heifers rather than lactating cows. A large percentage of dairy heifers are presently bred naturally while on pasture to bulls of questionable or unknown genetic merit. This is a dubious practice when one considers that the average dairy cow in the major dairy States, such as New York, produces an average of only 3.5 calves in her lifetime. If heifers can be grouped and their cycles synchronized, more of them are likely to be bred artifically to AI proven bulls.

Cycle synchronization of sheep and swine would result in more uniform lamb and pig crops, and better use could be made of facilities and labor. Lambings and farrowings could be concentrated in shorter periods of time, and in the case of swine the operation of multiple farrowing programs would be facilitated.

Estrous cycle regulation should be particularly useful in underdeveloped areas of the world where transportation and refrigeration facilities are limited and where management practices are such that the animals are not frequently observed.

Finally, estrous cycle regulation methods provide potentially useful new experimental tools. They can be used to improve the precision and simplify the operational details of many experiments in reproductive physiology and nutrition. They will likely provide the impetus for a large number of new experiments on ovum collection, storage, and transfer in domestic animals.

Numerous experiments conducted prior to 1960 (the year when the first experiment on estrous cycle regulation by feeding steroid hormones to ruminants were conducted) showed, in general, that effective cycle synchronization could be obtained in cattle, swine, and in cycling and anestrous sheep by various regimens of progesterone, estrogen, and gonadotropin injections. However, the conception rates re-

ported for animals bred at the synchronized estrus were usually quite low, and none of the methods tried appeared readily adaptable to widespread use under field conditions.

* * *

Since January 1960, estrous cycle regulation studies have been carried out at Cornell with 180 Holstein heifers, 555 Hereford and crossbred beef cattle, 816 cycling and anestrous ewes of several breeds, and 85 Yorkshire gilts. The results appear to justify the following conclusions:

(1) The orally active progestins, MAP and CAP, were both effective inhibitors of estrus and ovulation in cattle and sheep.

(2) Withdrawal of either compound from the feed resulted in effective estrous cycle synchronization in cattle and sheep. A high percentage of the treated animals came in estrus 3–6 days after hormone withdrawal.

(3) The minimal effective dose for cattle for MAP was approximately 200 mg per animal per day, and for CAP it was approximately 10 mg per animal per day. The comparable figure for MAP for ewes was 50–60 mg per day.

(4) The optimal length of the hormone feeding period for both sheep and cattle was 18–20 days.

(5) Group feeding of either compound in grain or liquid rations gave satisfactory results.

(6) The conception rates of groups of Holstein heifers bred artificially at the first estrus after feeding MAP and CAP ranged from 48 to 70 percent. These rates were generally below those obtained in untreated heifers bred artificially under optimal conditions.

(7) Conception rates in both control and MAP- and CAP-treated beef animals bred artificially were somewhat lower. In one trial with approximately 400 crossbred beef cows, conception rates to first service of approximately 40 percent were obtained for both control, and CAP-fed cows and 65 percent for MAP-fed cows.

(8) Conception rates of cycling ewes bred naturally at synchronized cycles following MAP feeding were slightly lower than rates obtained in control ewes.

(9) Dairy heifers, beef cattle, and cycling ewes failing to conceive at the synchronized estrus returned to estrus after normal cycle intervals and apparently normal conception rates were obtained at the second breedings.

(10) Synchronous estrous cycles and ovulations were induced in anestrous and anestrous lactating ewes with a combined PMS (750 I.U. injected on days 1 and 15) and MAP (60 mg per day fed on days 7–14) treatment. Conception rates to first service of 57 to 85 percent were obtained in ewes synchronized in this way.

(11) A sequential treatment involving an estrogen (MEE for 9 days) and progestin (MAP for 9 days) resulted in good synchronization and fertility in one group of gilts, but did not give good synchronization in a second group.

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MECHANISMS CONTROLLING THE FORMATION AND PERSISTENCE OF THE CORPUS LUTEUM

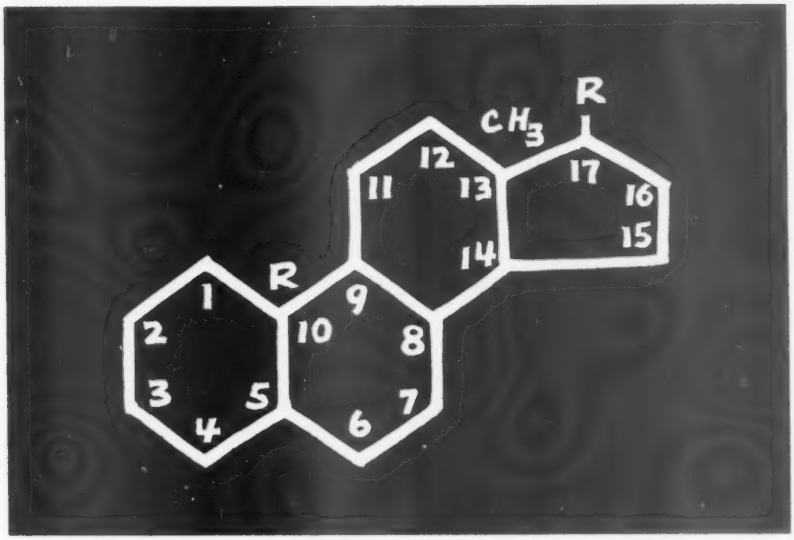
Mechanisms which control formation of corpora lutea during the estrous cycle, and particularly factors affecting their persistence and regression in various reproductive stages, have been of considerable interest to physiologists concerned with developing methods for control of the estrous cycle in domestic animals.

* * *

The mammalian ovary has two principal functions: the production and release of ova and the synthesis and secretion of hormones which regulate the reproductive tract and secondary sexual characters. These hormones also influence mating behavior and affect metabolism. Following ovulation, the wall of the ruptured follicle undergoes structural and functional changes, which transform it into a transient endocrine gland known as the corpus luteum.

While the early development of the corpus luteum appears to be quite similar in many mammalian species, the functional lifespan varies according to whether the animal is nonpregnant, pseudopregnant, pregnant, or lactating. In eutherian mammals it is generally accepted that the granulosa cells are transformed into luteal cells of the corpus luteum. The fate of these internal cells is less clear and there appear to be species differences as to their subsequent functional significance in the corpus luteum.

* * *



Results from recent investigations dealing with the comparative physiology of reproduction in rats, rabbits, guinea pigs, and ferrets, and particularly in sheep and pigs, have contributed to a better understanding to the mechanisms involved in the formation, maintenance, and regression of the corpus luteum.

In ewes and gilts the ovary is capable of ovulation when the pituitary is removed at or just prior to ovulation. An initial stimulus of a pituitary hormone(s) with luteotrophic action appears to be adequate for formation of corpora lutea. These corpora lutea are then maintained, according to morphological and histological criteria, for approximately the normal duration of the estrous cycle. The secretory function of these corpora lutea, which is the critical test, may not be quite the same. A predetermined luteal lifespan is indicated. In the cycling female the uterus maintains a positive inhibition of pituitary luteotrophin control which may be either humoral or neurohumoral in nature. In pregnancy and following hysterectomy, this inhibition is lacking in some species, hence the persistence of functional corpora lutea.[1]

Short [2] has proposed a system of dual control of the lifespan of the corpus luteum for the ewe by a pituitary luteotrophin and a uterine luteolysin. In this scheme a pituitary "on" mechanism would stimulate and maintain the corpus luteum lifespan, but perhaps not its secretory activity by a single release of a pituitary luteotrophin at the time of ovulation. However, the luteotrophin may be released into the circulation continuously. A uterine "off" mechanism would determine the length of the estrous cycle by providing a luteolysin. Of the two mechanisms, the uterine luteolysin would have the overriding effect.

It has been suggested that increased levels of progesterone may prolong the life of corpora lutea in the rat by maintaining secretion of a pituitary luteotrophin (prolactin, LTH).[3,4] Furthermore, the effect of hysterectomy in this species may be due to a deficiency or diminished secretion of LH, thus decreasing the luteolytic effectiveness of the pituitary gland.

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Creativity vs. the Organization Man

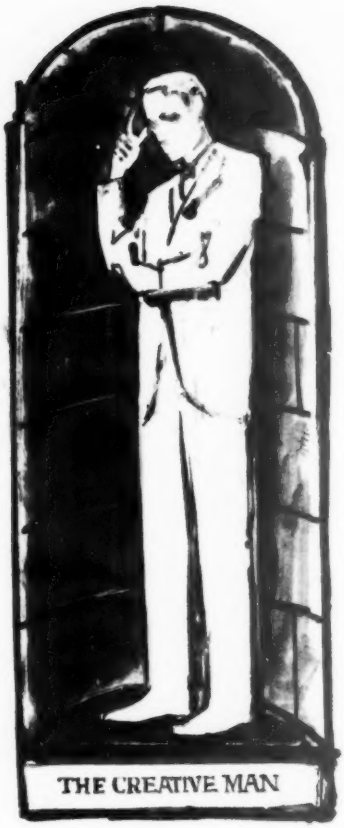
Nyle C. Brady

Let me first delineate the differences between the creative man and the organization man.

The creative man is concerned by his very nature with the unknown and with the future. He is responsible for creating entities that are unique, new, and without precedent. He is original; he is a divergent thinker. He is often a troublemaker. The statement has been made that all creative people are troublemakers. But certainly all troublemakers are not creative people.

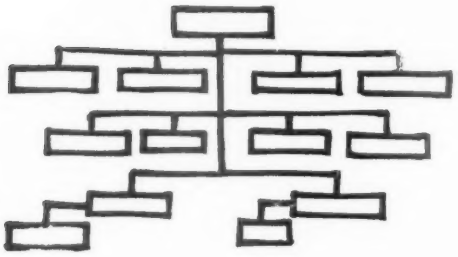
In contrast, the organization man is exemplified by conformity, which by its very nature looks into the past. The organization man reasons: "This is the way it's always been done; that's good enough reason to continue doing it this way. If I'm going to remain an integral part of this organization, I must conform." The organization man is a copier; he is not a troublemaker. He fits into the mold which society and his organization made for him. He is a convergent thinker. The boss likes him.

I can perceive trends in our society that have definitely encouraged the organization man over the creative one. As a result of our population explosion and the rapid expansion of cities, the lone individual becomes relatively meaningless as compared with the masses. Thus, the organization man, because he is not an individualist, fits best with his neighbors. Bigness of all aspects of our society—government, cities, universities, schools—demands organization, mass production, mass education. And stepped-up efficiency tends to demand conformity.



Obviously, the organization man is encouraged by the social pressures for conformity and the rewards for fitting into the mold. He would choose the emphasis on security which conformity offers rather than the principles which creativity demands. Even our educational system encourages conformity. Results of psychological tests uphold this view. I've been told that tests in elementary schools show that

This paper is adapted from a talk which Dr. Brady made at a meeting of OPEDA (Organization of Professional Employees of the Department of Agriculture) held at Beltsville, Md., May 12, 1964.



the degree of creativity tends to decline as youngsters reach the fourth or fifth grade. They no longer desire to be different; they would rather follow their classmates than do what they think is basically right or what their native creativity might dictate.

Our empirical and bureaucratic uniform procedures of operation and personnel advancement discourage creativity. If we work out a system that is efficient, we find that conformity is a concomitant feature of the system. In many instances we downgrade the individual because the well-being of the group and the organization is more important. What the individual does, therefore, becomes relatively insignificant.

CREATIVITY AND SCIENCE

Certainly I need not reiterate the significance of the individual in the world of science. Even a relatively few creative men can make one research division stand out compared with another. The major scientific advances have been made by a rather small group of creative men and women. The others fill in the chinks, polish off the roughness, and clean up the mess after the breakthroughs have been accomplished.

A recent personnel study among the various research and education agencies in the Department of Agriculture has revealed some wide differences in the ratio of Ph. D.'s to degrees of lesser rank. Although it would be foolish to assume that the agency with the highest proportion of Ph. D.'s would rank highest in creativity, I believe its chances would be improved, particularly if a few of those Ph. D.'s were nonconformists. The greatness of any research institution is determined primarily by the greatness of its individual scientists, and in some cases by the greatness of a very, very small group of creative, yet dedicated, scientists.

USDA STUDY

The major purpose of organization and administration in any research and educational agency is to provide the proper environment and support for the individual scientist. Here in the Department of Agriculture, we have been told by competent outside study groups that the environment and opportunity for growth of individual scientists are not what they should be. It has been said that there is a tendency to use the number of years of service as the overriding criteria for advancement and position in the Department. There may be a tendency to pull leadership from the top of the barrel, so to speak. We may say that because a certain research worker has been here longer than any other one, he's more entitled to a leadership position, even though another one with less service may be more

competent. Undoubtedly, this attitude is not limited to the Department of Agriculture. But the stigma is upon us.

We are now attempting among ourselves to take a realistic look at this situation. A group of 16 people—half of whom are working scientists—is making an in-house evaluation of the environment our scientists work in and the opportunities they have to improve themselves. We believe that scientists themselves are the best judges of research quality in their field of competence, and that as a consequence they should be given ample opportunity to judge that competence and let their judgment be heard. Despite criticism of this plan, I believe that the only way we can evaluate need and effect changes will be through an evaluation by men who have the responsibility for carrying out the job and not by those who are less intimately concerned with the research program. With this group, therefore, we place our hope that an understanding appraisal will lead to opportunities for improving the environment of our scientists, if, in fact, it is not what it should be.

Now, what is the role of administration in relation to creativity? This is an area that cannot be ignored because it affects everyone, directly or indirectly. To discuss it and analyze it intelligently, we need first to examine the two basic methods for funding research within the Department of Agriculture and the land-grant universities: (*a*) through institutional grants such as Hatch formula funds, and (*b*) the competitive grant method.

INSTITUTIONAL GRANTS

The traditional institutional grant has been exemplified by that used by the USDA and particularly by the land-grant universities. With this method, the agency and the administrator control the budget and to a considerable degree the program. A strict project accounting system provides a record of research underway. This method gives a continuity of funds; that is, a fairly reliable guarantee from year to year that funds will be available to continue the same research or to change it as necessary.

Generally, research under this system is mission oriented. In some respects this is good because it assures that the work done is that assigned to the agency. On the other hand, it tends to put the guiding of research programs in the hands of administrators, legislative bodies, and sometimes pressure groups. Even so, the intent is that the research is geared to the needs of people and not just those of the scientists. Thus it is part of a democratic process of fund distribution to States and projects, but it does not necessarily allocate funds in relation to the competence of the scientist.

The institutional grant system does have its disadvantages. The scientist may have too little to say about the program and the budget; he often plays a minor role in decisionmaking. Moreover, basic research is frequently deemphasized at the expense of applied research. There is often too little emphasis on quality as a requisite for granting funds. This system tends to become calcified and resist change because of the lack of competition. Unless their populations change, State A may receive the same amount of money as State B year after year regardless of any difference in competence of their respective scientists.

COMPETITIVE GRANTS

The more recent, science-oriented control program—the competitive grant (or contract) method—is being used by a number of agencies such as the National Institutes of Health, the Atomic Energy Commission, and the National Science Foundation. Here, the scientist is the focal point in determining both program and budget. He is inclined to refer to "his" program and "his" graduate assistants rather than the university's program or personnel. Whether we like it or not, in many instances it appears that such grants are made to individuals, through institutions, which sometimes become mere holding companies for the scientist.

In a recent document prepared by a committee studying this dichotomy of fund control, a statement appeared that the grant is made to the institution. Yet in the very next sentence the scientist is told that he has to make up his mind as to whether or not he will accept the grant. Obviously, a grant cannot be made to an institution if the scientist is the one who has to accept it.

The competitive grant method of funding research has both advantages and disadvantages from the standpoint of total contribution to the program and from the standpoint of creativity.

On the positive side we can point to the fact that funds are presumably concentrated in areas where the best scientists are located and not wasted in institutions where competence is lacking. In other words, the competitive approach is emphasized, and this has its good aspects. For one thing, it encourages creativity and sets up opportunities for a man to do what he wants to do in the interests of good research. Academic freedom is maximized. The scientist controls his program and is in a position to promote his own budget. Generally, there is a tendency for the more competent—and perhaps the more creative scientist—to get more funding.

Under the competitive grant method, basic research usually gets good support without having to hide under the guise of being applied research. It is supported wholeheartedly as basic research.

What are some of the disadvantages of this method? A scientist must become the promoter, the administrator, the lobbyist as well as carrying out his normal role. And because they are human, some scientists enjoy these added duties. They're important people not only in the laboratory but elsewhere. Sometimes the program is selfcentered in the scientist's small kingdom, and he has little, if any, interest in coordinated research. He sees no real advantage in working with anyone else unless the group is small and has the same kind of interests as his. Such an attitude brings about a complete breakdown in broad areas of research where coordination is vital.

Lack of fund continuity provides little opportunity for longterm planning, and, in many institutions, no job security for younger scientists. As a result we have the perennial postdoctoral fellow. He comes in to do postdoctoral research, works 2 or 3 years, and likes it so well that perhaps when another grant comes along, his salary has increased to the point where he can't afford to take a job elsewhere at the beginning scientist's salary. Consequently he stays on. In many institutions this is becoming a real problem, because the postdoctoral fellow is competing with the graduate student.

In the competitive grant system, the authority of the university over its faculty is weakened. Teaching duties are sometimes relegated to a secondary position. This ability to compete for research grants determines a professor's supposed value to an institution. This often results in his receiving outside offers with a guarantee of no teaching and absolute freedom in his research. In such a circumstance, the administrator has no recourse but to offer the professor comparable benefits, assuming, of course, that he wants to retain him on the staff. Thus, the administrator loses primary control of the research in this area and teaching, especially that of undergraduates, suffers. Today, university scientists are seeking jobs that require little if any teaching. I am sure teaching suffers because it lacks the glamour that surrounds research. And, unfortunately, activity in the classroom offers no comparable motivation to that found in research.

A COMBINATION

What, then, is the best approach in the administration of a research program? I believe each method that I've described has desirable features which should be retained. A middle-of-the-road approach would provide a continuation of broad-based research support through formula allocation for the States and problem-oriented, in-house research for the Department of Agriculture. This would provide continuing support for the agricultural research potential of both the States and the Federal Government. But, in addition, we need an expanded competitive grant program using the quality of both project and investigator as a basis for funding. Furthermore, this program should have support through the Department of Agriculture so that it can be coordinated and integrated with the "in-house" research programs of the State and Federal agencies. Our better scientists should not be forced to look to sources other than agriculture for funds to support high-quality basic research.

Recently the Cooperative State Research Service received 376 project proposals from 49 of the 53 State agricultural experiment stations in response to an invitation to submit project proposals for a particular area of research. Seventy-two projects in 31 States were judged to be outstanding in quality of proposal and competence of the investigators. Unfortunately, we had funds for only 27 of the 72 projects. Although these funds were granted on a competitive basis, we were cognizant of the need to make an equitable distribution among the States insofar as possible.

By this method, grants will continue to be made to institutions and the administrators will have the fiscal responsibility for fund expenditures. But the competence of the scientist will be a major factor in determining which institutions get the money. Under the competitive grant procedure only basic research can be supported at the present time, but modifications may be possible in the future to permit the support of applied research.

Within the Department of Agriculture I believe there may be opportunity for greater participation by the creative scientist in making basic decisions about research programs. Sometimes the administrator is a long way from the working scientist and his problems. In my opinion, we should take a serious look at whether or not we are giving the scientist ample opportunity to take part in decisionmaking that may affect his future and that of his profession.

In our desire to give the creative scientist greater voice in determining the course and nature of agricultural research, we should not give the impression that *all* scientists are creative and that *all* administrators lack creativity. Evidence will show that frequently the opposite is true. We have some very capable research administrators at both the Federal and State levels. Furthermore, they are often more creative and less resistant to change than are their counterparts among the scientists. Our aim should be to give credence to creativity over conformity wherever it is found.

Undoubtedly there will be resistance on the part of many to move away from the current "safe" system. There will be problems resulting from the comparable bidding power of small and large institutions to carry out research work, and from main laboratories and field laboratories in the Department of Agriculture. There will be reluctance among research workers to break away from the 8-to-5 routine, the long-established seniority pattern, the security of conforming to the pattern of the organization man. Although there is plenty of room for organization men, I can't help feeling that there has been a tendency to smother the creative man, to make him fit into the mold whether he likes it or not, to deny him the right to participate in decisionmaking. We need to encourage more creativity, and I am hoping that we can develop some forces within our organizations that will move in that direction.

* * *

A Humble Scientist

The other day I received an annual report from one of our Agricultural Research Service cooperators. In his letter of transmittal, he said, "This is a meager contribution indeed toward the needs of the area, but it represents the best effort of which we are presently capable."

The scientist making this report is a young man and, on the basis of his message of transmittal, I predict that he will go far in his chosen field. In the first place he has an appreciation of the vast unknowns existing in his field. Second, he has the humility to realize that what he discovers will be meager when contrasted with the undiscovered. Third, in spite of the fact that this is true, he is putting forth his best efforts. Fourth, he implies that he is going to be more capable in the future.

Appreciation, humility, dedication, and ambition—to me those are fine attributes for a research worker to possess.

To show all of these desirable traits in one sentence also indicates a talent in the art of communication which is another desirable trait in a researcher.

Incidentally, the report was excellent.

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Meat Tenderness

Milton E. Bailey

Even though past study by many investigators has contributed much basic knowledge concerning meat tenderness, the precise causes for many variations reported remain obscure. A survey of past literature reveals the paramount need for intensification of effort and study of the biological and physicochemical interrelationships which influence this important quality attribute of meat. Precursory to adequate study of the many relationships involved is agreement of what meat tenderness really is and how it might be measured.

Tenderness of meat is a psychological interpretation of a physiological response to physical-chemical stimuli caused by chewing meat. It differs from other quality attributes of meat in that it involves the ease of mastication by teeth. Food texture can be measured to some degree by physical or chemical methods, but tenderness, per se, is translatable only in terms of human perceptions from certain meat characteristics. Consequently, only the sensory panel consisting of human subjects can effectively measure meat tenderness. For this reason, results obtained by the sensory panel are nearly always used as a point of reference, and almost without exception, are a mode of comparing meat tenderness.

Classic studies have indicated that wide ranges in tenderness exist among muscles in any one animal. In general, it might be said that those muscles containing large amounts of connective tissue are less tender than those containing smaller amounts of connective tissue. This has been the dogmatic response to explaining differences in meat tenderness even though quantities of connective tissue are small compared to the content of other muscle proteins. Certainly, there must be some relationship between tenderness of muscles and their anatomical function in the live animal and this would be reflected by quantities of connective tissue present. This was demonstrated by Ramsbottom and coworkers (*13*)[1] who clearly showed a progressive increase in tenderness of muscles having little use relative to those requiring extensive use during animal movement.

ANIMAL AND MUSCLE VARIATION

Causes of meat tenderness are extremely complex and many factors influence tenderness. Undoubtedly, individual animal variation, where all overt character is apparently constant, is partly responsible for lack of agreement among similar studies.

[1] Italic numbers in parentheses refer to "Literature Cited," p. 34.

Unfortunately, most studies involving beef are self-limiting because of the expense of working with meat from these animals. It is often difficult to study sufficiently large numbers of any one variable to reach definite conclusions. This has been a perplexing problem for many investigators.

Research in Europe and other foreign countries generally involves more exhaustive study of even fewer numbers of animals, and though this approach is more informative of the particular animals used, these studies are often cursory in predicting quality of other animals.

SENSORY ANALYSIS

With any discussion of food quality, including tenderness of meat, the method of evaluation becomes important, particularly when organoleptic panels are employed. Two types of panels are used in tenderness studies, a consumer preference panel and a trained panel. An adequately trained taste panel can discern differences in tenderness with great objectivity and reliability, and results obtained can often be quantitated. In past studies of meat tenderness, however, too little attention has been given to training and standardization of panels, and this accounts for some of the wide differences of opinion concerning causes of tenderness variations.

Perhaps the most precise study of subjective tenderness has been that of Cover (2) who described tenderness in terms of softness to tongue and cheek, softness to teeth pressure, fragility of fibers and connective tissue, and residue remaining following standardized chewing. This approach to subjective analysis of meat tenderness, along with stringent detail regarding panel training and their motivation as well as attendant problems such as length of testing session, arrangement of stimuli within the test and cooking procedures should do much to make tenderness data more reliable and more comparable.

Meat can be made tender by grinding, pounding, prolonged aging, or hydrolyzing constituent proteins with proteolytic enzymes, but our discussion is limited to inherent differences in tenderness between intact cuts of meat such as steaks or roasts. The ultimate determinant of meat tenderness of these cuts is the physical and chemical state of muscle components at the moment of consumption. It is impossible with present knowledge to say what factors are most important in determining tenderness of a specific piece of meat. The most important elements studied by past investigators include: (1) Inheritance and sex, (2) chronological age, (3) livestock management, (4) post mortem aging, and (5) methods of heating and cookery.

Obviously, the causes of tenderness or lack of tenderness cannot be resolved without study of all of these variables as well as others, and although numerous contributions to the literature have been made, there is little agreement concerning their relative importance. Many aspects of these variables of meat tenderness have been discussed in recent reviews and symposia (*1*, 3–12, and *14*) and these references provide detailed information concerning various aspects of meat tenderness.

INHERITANCE AND SEX

Tenderness appears to be a heritable trait, but tender as well as less tender meat is found in animals of all breeds. The relation of breed with beef and pork tenderness has recently been reviewed by Palmer (*9*) who cited data which support the belief that breed of sire had a pronounced effect on tenderness. He was able to group progeny within each breed according to differences in tenderness. Many differences in meat tenderness attributable to breed have been indicated, but in numerous studies, differences between sires within a breed far exceeded those due to breed. It should then be possible to select sires within breeds and species which have potential to transmit desirable tenderness traits to their offspring. These traits could be maximized through use of appropriate environmental conditions. The major obstacle in determining heritability effects on tenderness by progeny

testing is that only slaughtered animals can be tested. Also, progeny testing is time consuming and expensive. Despite these restrictions, progress is being made and several stations have initiated long-term breeding studies which should contribute important findings to this important aspect of meat tenderness.

Relatively little data have been published concerning effects of breeding on tenderness of pork or lamb. Today's demand for the "meat type hog" has possibly increased concern regarding lack of tenderness in some fresh pork cuts such as loin, picnic, butt, and ham, but these have been studied insufficiently.

Undoubtedly many differences in tenderness attributable to breed are due to sex-breed interactions and not due to breed alone. This raises the question of the importance of sex in determining tenderness of meat. The major problem in this respect relates to differences between steers and heifers and between barrows and gilts. It is generally assumed that animal sex within these limitations has little effect on tenderness and that implantation of diethylstilbesterol has only minor effects on tenderness even though growth and fat deposition are influenced. Most striking are the results (*15*) that meat from young steers is only slightly more tender than that from bulls of the same age. Bulls were more effective in converting feed to meat and produced less waste. Trends today indicate that this will be an important economic factor in the near future.

The recent impetus on use of lean meat has increased studies of bull and boar meat. These studies, in some cases, have indicated that the tenderness of young bull and boar meat is acceptable and often indistinguishable from that of steers and barrows. Classic differences in tenderness between meat from bulls and boars relative to gonadectomized animals are probably in part due to age and not to sex, and it has been reported that age is more important than sex or the effect of castration on tenderness of beef (*14*).

CHRONOLOGICAL AGE AT SLAUGHTER

Maturity of the animal at slaughter apparently influences tenderness. Meat from veal and calf is usually considered more tender than that from beef, and meat from the latter is usually more tender than that from mature cows or bulls. Palmer (*9*) referred to several investigations which supported the theme that tenderness decreases with increased chronological age. His own data, however, did not substantiate these claims. Working with 538 carcasses from calves, steers, heifers, cows, and bulls ranging in age from 5 months to 99 months, he found that age accounted for only 6 percent of the variation in tenderness. Much higher correlations were obtained between tenderness and age of animals whose carcasses were devoid of marbling relative to more highly marbled carcasses, indicating that the interaction of age and marbling may be more important than age alone.

LIVESTOCK MANAGEMENT

Important considerations concerning the influence of feeding and management on meat tenderness include the degree of marbling resulting from feeding and the rate of growth and development due to feeding.

The former consideration has been a point of discussion by many past workers. Some ramifications of this problem have been discussed recently (*1*) and study of approximately 2,600 cattle by various workers mentioned. Direct comparisons of results from these studies were difficult because of the different experimental designs employed. Samples used in determining tenderness came from muscles of several anatomical locations within the beef carcass; there were also many variations regarding aging, storage, types of cookery, and degree of doneness. Also, estimations of marbling were made by several different methods. The contribution of marbling to tenderness found during these studies ranged from 0.01 to 36 percent, and prorated according to sample numbers, the value was approximately 5 percent.

We can only conclude from this interpretation of results that marbling in beef is insufficiently correlated with tenderness to be considered an index of this quality attribute. However, intramuscular fat apparently has some influence on tenderness. Most data reported in the literature indicate a low but positive relationship between marbling and tenderness. Slight amounts of marbling of beef seem desirable, but beyond a certain degree marbling appears unrelated to tenderness.

Results from study of fat and tenderness of pork are more conflicting than those obtained from beef studies, and there is no general agreement concerning the influence of marbling on pork tenderness. It should be pointed out, however, that intramuscular fat may enhance certain other properties of meat palatability that are not completely divorced from tenderness. Fat may act as a lubricant and thus affect ease with which meat is masticated or swallowed; it may stimulate salivation and it may influence overall flavor.

It is difficult to visualize extreme changes in tenderness due to feeding of individual nutrients or other additives, but feeding of well-balanced diets relative to other types of feeding will enhance growth rate and expedite gains. Animals fed balanced diets in adequate amounts should reach market weight at a nearlier age and this could influence their ultimate tenderness, although some published data do not concur with this reasoning.

Present methods of beef grading may be subject to criticism after examination of many results concerning fat, age, and tenderness. Carcass grade is not always closely related to tenderness or other palatability factors, particularly in the lower grades (*4*). Even though imperfect as an indicator of tenderness or other palatability factors, the grading system has served a useful purpose for many years and will continue to do so until replaced by more objective methods contingent upon the understanding of many complicated factors presently subject to controversy.

POST MORTEM AGING

In aged meat, factors other than fat are believed to be responsible for tenderization (*4*). Some of the biochemical changes occurring in muscle in the time between death and onset of rigor mortis are known. These involve decreases in glycogen, pH, adenosine triphosphate, and increases in lactic acid, ammonia, and the formation of "actomyosin." The latter change results in an inflexible toughened muscle. The precise biochemical change of meat occurring following rigor mortis in various aging environments that bring about tenderization in some instances have not been elucidated. Theories proposed include: (*a*) dissociation of "actomyosin," (*b*) changes in connective tissue, (*c*) proteolysis, and (*d*) increased hydration of proteins.

It seems logical that the physical events associated with actomyosin formation during rigor would be reversible since the process is so similar to muscle contraction, but seemingly this is not the case. It appears that rigor mortis as it occurs in meat during aging is an irreversible process even though further contraction might be stimulated by adding adenosine triphosphate (*10*). Likewise, there appears to be little change in connective tissue content during aging, and if changes do occur, they are sufficiently minute to be undetectable. Conversely, numerous investigators believe that meat is tenderized during aging by some form of proteolysis or that increased hydration might be responsible for changes in muscle proteins which alter their tenderness.

Proteolysis could be catalyzed by autolytic enzymes of muscle (cathepsins) or by proteases produced by bacteria, even though the latter possibility is more remote due to the relative sterility of internal meat tissues during aging. There is little doubt that cathepsins are present in beef muscle, but their specificities and their role in tenderizing meat are unknown. Present belief is that cathepsins and similar hydrolyases are localized in intracellular particles called "lysosomes" and the fragility of these may be important in determining chemical changes during aging. Lysis of these particles followed by increased autolysis of tissue constituents by hydrolyzing enzymes may be a future approach to tenderizing meat, either at conventional or at higher temperatures.

Following integrated study of the relationship between biochemical changes and tenderness during aging, Deatherage (*3*) has concluded that degree of hydration of muscle proteins is important, yet in many studies tenderness and juiciness have not been parallel. This aspect of muscle tenderness has been reviewed exhaustively by Hamm (*5*), another proponent of this theory. Water-holding ability of muscle proteins varies in meat and certain factors that affect this property also contribute to tenderness.

The physiological condition of the animal at slaughter is responsible for chemical changes which govern water-holding capacity. Of major concern is the susceptibility of animals to stress and the consequent result of stress on anaerobic glycolysis immediately before and following slaughter.

Certain types of stress create high demands for phosphocreatine and adenosine triphosphate under anaerobic conditions which results in high lactate production. If the stress condition stimulates glycolysis ante mortem and permits diffusion of lactate to blood and its removal during exsanguination, ultimate muscle pH will be higher than normal and the constituent proteins will have greater water-holding capacities than normal muscle proteins. If the stress condition (usually immediately prior to death) prevents lactate removal from muscle during slaughter or if it stimulates rapid glycolysis following slaughter, pH will decrease rapidly post mortem. Hydrogen ion concentration approaching the isoelectric point of muscle proteins will diminish water-holding capacity as would the combination of relatively high temperatures and high hydrogen ion concentrations post mortem.

The result of the former type of stress would be enhanced water-holding capacity which should increase tenderness, while the latter type of stress would lower water-holding capacity of meat and should decrease its tenderness. Soft, watery pork is an example of meat having decreased water-holding capacity, and dark cutter beef and high pH pork are conditions that enhance water-holding capacity of meat. Heating of meat during cookery releases juices proportional to the amount of heating, but soft, watery pork would lose a greater percentage of moisture than would meat from high pH pork. These moisture losses would certainly influence relative tenderness of these samples. Most published data support these contentions.

EFFECT OF HEATING AND COOKERY

Any useful attempt to study meat tenderness must consider not only the structural variation of the animal tissue and the post mortem changes during aging and other processing, but also changes resulting from heating. Since tenderness is a quality of cooked meat and not raw meat, the type of cookery is an extremely important aspect in determining tenderness.

In meat cooked to a rare degree of doneness, muscle fiber proteins are tender and connective tissue is tough. Those cuts having greater quantities of connective tissue will usually be less tender than cuts having lesser amounts of connective tissue. One type of tissue usually overlooked in this regard is that surrounding individual muscle fibers consisting of endomysial collagen, fine elastic fibers, reticular fibers, and the sarcolemma.

In investigations of chemical causes of tenderness, precise description of changes in these and other tissues during cookery are imperative. Exact knowledge of the effects of heat on constituent protein is necessary. Newly developed procedures such as differential thermal analysis of muscle proteins

should add much to these studies, but fundamental cookery investigations remain important. The effects of cookery and heating on meat proteins have been reviewed respectively by Paul (*11*) and by Hamm (*5*).

Type, rate, and temperature of cookery are all important in determining tenderness of meat. The most effective procedure for tenderizing meat is one resulting in a maximum amount of connective tissue degradation or softening and minimal amounts of muscle fiber toughening and juice loss. Information is accumulating regarding the desirable effects of heating at lower temperatures during longer periods to reach the desired degree of doneness.

It has often been said that any piece of meat can be made tender through use of the appropriate method of cookery. Eventually, individual cuts may be retailed with specific instructions regarding cookery, but this remains for the future Our dilemma arises from the inability to predict tenderness of individual pieces of meat. *This is our ultimate goal.*

EMPHASIS ON COORDINATED AND INTERDISCIPLINARY RESEARCH

There is little doubt that most factors mentioned above in some way influence tenderness, but knowledge of these influences is inadequate. Integrated effort by groups of workers interested in the physiology, anatomy, genetics, and management of animals and the biochemistry of meat is urgently needed before the relative importance of specific factors on the actual eating characteristics of meat can be determined. Collaboration by some of our colleagues in various research disciplines by using the European approach to detail, and carefully controlled, well-coordinated regional projects that would allow study of large numbers of animals over long time periods would be a step in the right direction.

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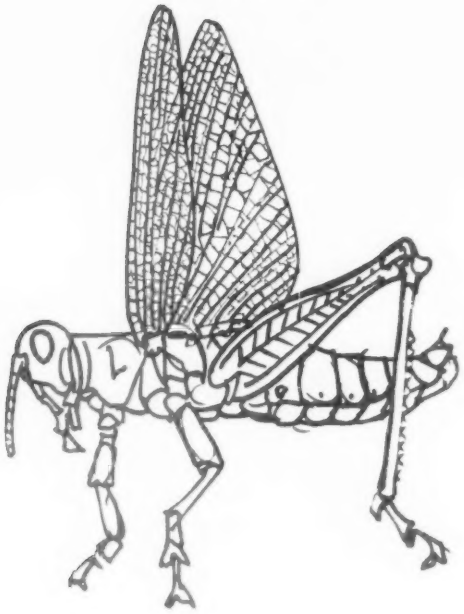
Donald R. King



The Turning Point in Entomological R

Entomological research is entering an age of discovery, the beginning of which was marked by the development of synthetic organic insecticides and their spectacular control of harmful insects. Since then, new ideas that germinated in the minds of research scientists were nurtured in the attendant problems of residues and insecticide resistance. Actually, many of the "new" research approaches are not new at all. Some of them were conceived and investigated in the early days of entomological research, but, for various reasons, remained in a somewhat dormant state. Other approaches developed as our knowledge of insects increased during the chemical control period. Many of them followed developments in other disciplines. In any event, the changing needs of society have brought us to the point where new methods of warfare on insects are mandatory.

Perhaps the most striking and significant of the new methods of warfare is the sterility technique. Knipling (*11*)[1] presented an excellent account of the progress achieved by the use of this control method. The following excerpts from his discussion summarize the principle and status of insect sterility research.

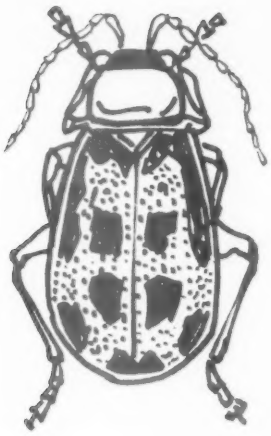
"When individuals in an animal population are killed, the only effect on the population is the elimination of those actually destroyed. When animals are sexually sterilized, without adversely affecting sexual competitiveness, the following effects are possible: (1) Those sterilized cannot reproduce—an effect equivalent to killing. (2) Sterile organisms compete with the fertile organisms and further reduce the reproductive potential of the population. . . . (3) The sterility method has a potential time effect."

In addition, sterile insects can affect reproduction throughout the normal range of dispersion of the sterile individuals—a "space" effect.

As Knipling pointed out, the sterility principle will not be applicable for all insects or even a majority of the destructive species. But successes to date indicate that future development will broaden potential usefulness.

This last statement characterizes much of the thinking in entomology today. As one example of the newer, imaginative approaches to control problems, research entomologists are considering the feasibility of releasing insects contaminated with in-

[1] Italic numbers in parentheses refer to "Literature Cited," p. 41.



cal Research ...

sect pathogens or those carrying a genetic complement which will adversely affect the natural population.

Biological control research also has assumed a new stature and offers real promise. There are several reasons for this. Under ideal conditions, natural enemy populations increase as host numbers increase; thus the number of natural enemies is proportional to the pest population. Also, insect parasites and predators have the ability to seek out and destroy pest species without creating insecticide residue or resistance problems. Because of these advantages, entomologists have a largely unexplored area of research available in the increase and dissemination of endemic predators and parasites. The importation and liberation of foreign natural enemies of insects and noxious weeds is another promising field. Recently, for example, Coles and Puttler (*8*) reported that five imported parasites of the alfalfa weevil have become successfully established in the eastern United States. Undoubtedly they will exert a significant influence as their numbers increase.

The effects of insecticide applications on natural enemy populations and the possibility of developing insecticide resistance in beneficial insects are also areas for future investigation. Smith et al. (*17*) recently reported that their culture of a predaceous mite apparently had developed resistance to DDT. Tests with these and other mite species disclosed that the predaceous mites were less affected by applications of certain chemicals than the phytophagous mites upon which they fed. Bartlett (*4*) assessed the effect of 61 pesticides on 5 hymenopterous parasites and 6 predatory lady beetles and noted considerable variation in the effects of the chemicals on these insects.

As a result of this type of research, it has become apparent that integrated control programs may be developed in which insecticides are used in such a manner as to take advantage of the partial protection afforded by biological control agents. For example, Quist and Anderson (*16*) suggested that peachgrowers in western Colorado avoid applying insecticides at the time that an effective peach twig borer parasite is most active, and recommended a preferred type and timing of treatment. The use of systemic insecticides also may reduce the frequency of application, particularly if complete pest kill is not accomplished, leaving a sufficient reservoir of host insects for beneficial insect survival. It is probable that insecticide resistance is less likely to develop in pest populations that are under pressure by natural enemies.

As a word of caution, there is some doubt as to whether or not pest population increases following insecticide applications are due entirely to natural enemy destruction. Research is needed on the complex ecological changes that follow application.

Unfortunately, beneficial insects cannot be used to solve all our entomological problems. Their usefulness appears to lie principally in maintaining steady pressure on pest populations on crops in which some insect damage can be tolerated. However, in some instances, natural enemies have been phenomenally successful and, in the course of time, have all but eliminated host populations.

Increasing interest is developing in the use of micro-organisms for insect control (*1*). For some time, the view has been held that pathogenic agents such as viruses, bacteria, and fungi are normally present "in the field," but are effective only under very specific environmental circumstances. This may not always be true. In early experiments in Massachusetts, Bartlett and Lefebvre (*5*) were able to cause significant reductions in European corn borer populations in 2 successive years by distribut-

ing an entomophagous fungus. Pimentel and Shapiro (*15*) later reported that variations in relative humidity, exposure to continuous light or darkness, low concentrations of certain poisons, and starvation had no effect on the severity of a virus infection of the greater wax moth, although exposure to ultraviolet light and diet variations increased susceptibility.

Research is demonstrating that there are strains of micro-organisms of varying virulence which are effective under a wide range of environmental conditions. Chronic infection of an insect by one strain or species of pathogen may increase or decrease host susceptibility to another. Recently Aruga et al. (*2*) reported that feeding small amounts of one virus to silkworms prevented disease occurrence from another subsequently administered virus. The selection of exceptionally virulent strains of micro-organisms which may be used singly or in combination with others producing different disease symptoms in a pest species has tremendous possibilities.

Although micro-organisms will not provide control of all our injurious insects, results obtained in recent concerted attempts to utilize them demonstrated much promise. It may be that host resistance to disease-producing organisms will develop as it may also for chemosterilants.

Research in physiology is providing our first consideration of the possibility of interference with the hormonal control of insect life processes. Wigglesworth (*19*), for example, reported that a hormone-like chemical was effective in preventing metamorphosis in the bug, *Rhodnius*. Biological triggering mechanisms such as photoperiod, diurnal rhythms, and temperature are being painstakingly explored and, with ecological studies on population management, may lead to the prediction or prevention of insect outbreaks (*12*). The tangled thread of developmental biology—what makes the insects grow, diapause, metamorphose—is gradually being unraveled. The implications of this research are barely comprehended. It is a field which remains virtually unexplored.

Table 1.—Man-years of entomological research at State experiment station (S) and ARS (F) according to kinds of insects and subject-matter areas, 1963

Kinds of insects and subject-matter area [1]	Basic biology, physiology, nutrition		Cultural and insecticidal control		Insecticide residue determination		Biological control	
	S	F	S	F	S	F	S	F
	Man-years		*Man-years*		*Man-years*		*Man-years*	
Vegetable insects	9.6	4.9	19.6	7.2	5.7	6.4	3.8	3.9
Fruit and nut insects	17.8	8.2	25.9	[2] 13.2	3.5	4.4	6.0	4.0
Forage and range insects	19.7	4.0	8.5	5.0	5.2	5.3	3.2	3.9
Soybean, peanut and sugar crop insects	1.5	1.3	1.8	2.2	.5	1.3	.4	1.2
Corn, sorghum, and small grain insects	12.7	9.5	7.4	4.8	3.2	3.2	.7	3.6
Cotton insects	8.0	22.0	8.6	18.4	.....	.....	1.4	5.2
Tobacco insects	.7	1.1	3.0	.6	.3	.1	.3	.8
Ornamentals and turf insects	5.1	0.6	9.8	2.5	.2	.....	.....	1.1
Livestock insects	4.3	13.6	6.8	9.0	4.0	4.9	.9	.5
Poultry insects	.2	.4	.7	.9	1.9	.2	.....	.....
Man, household, industrial insects	3.6	3.1	1.4	9.1	.....	.....	.4	.7
Stored products insects	.....	.....	.....	.....	.....	.....	.....	.....
Apiculture	.....	.....	.....	.....	.....	.....	.....	.....
Analysis, synthesis, formulation, and evaluation of insect control chemicals	.....	.....	.....	.....	.....	.....	.....	.....
Taxonomy	.....	.....	.....	.....	.....	.....	.....	.....
Exploration, introduction and evaluation of of biological control agents	.....	.....	.....	.....	.....	.....	.....	.....
Insect pathology	.....	.....	.....	.....	.....	.....	.....	.....
Insect physiology and toxicology	.....	.....	.....	.....	.....	.....	.....	.....
Total	83.2	68.7	93.5	72.9	24.5	25.8	17.1	24.9

[1] In addition to the ARS research program, there are 81 man-years of research on forest insects in USDA Forest Service (Division of Forest Protection Research) and 20 man-years in the State experiment stations.

A glimpse of the promise of another area of research is provided by recent studies of light and chemical attractants. Results of studies on sex attractants are discussed on such widely varying insects as the introduced pine sawfly by Casida et al. (*7*) and the American cockroach by Yamamoto (*20*). Host attractant principles also have been discovered. Kamm and Fronk (*10*) have found 38 compounds in alfalfa that are attractive to the alfalfa seed chalcid and 9 that are repellent.

Attractants appear to hold their greatest promise for luring injurious insects to specific areas where they may be treated with chemosterilants and released, or destroyed with insecticides at greatly reduced application rates. Also, it may be possible to develop methods of attracting beneficial insects to pest infestation. Conversely, repellents may be used to prevent infestation in particular areas.

Prerequisite to much of the recent progress in entomology has been the development of mass-rearing techniques which not only provide insects for mass-release programs but also furnish large numbers of individuals for year-round research. This development has been of fundamental importance. Studies of insect nutrition with artificial diets have evolved from mass-rearing attempts. For example, Vanderzant (*18*) determined the effects of several amino acids on boll weevil oviposition. As the nutritional requirements of insects are better understood, we may learn what chemicals and what concentrations of them are necessary to disrupt physiological processes and how they may be used either directly or through resistant plants and animals.

There is increased research activity recently in developing plant resistance to insects. Barnes (*3*) reported that spotted alfalfa aphid populations were 5 to 13 times greater on susceptible varieties of alfalfa than on the resistant variety Moapa. Bottger et al. (*6*) determined that cotton varieties with high gossypol content in the leaves were less susceptible to insect attack. Although insect strains may appear which will develop on resistant plants, this control method undoubtedly will continue to

Insect sterility attractants, baits		Evaluation of detection and control equipment		Varietal resistance of plants to insects		Insect vectors of diseases		Total all areas	
S	F	S	F	S	F	S	F	S	F
Man-years		*Man-years*		*Man-years*		*Man-years*		*Man-years*	
2.0	3.0	1.2	2.2	3.4	1.8	8.8	2.1	54.1	31.5
2.4	13.0	1.7	2.0	3.8	.6	7.1	4.6	68.2	50.0
1.6	.8	.8	.5	2.6	5.3	1.2	1.0	42.8	25.8
1.9	1.0	.....	.1	.8	.6	.8	1.8	7.7	9.5
1.3	2.3	.....	.5	5.0	10.9	1.7	2.3	32.0	37.1
1.9	8.3	.....	1.3	1.6	2.7	.....	.....	21.5	57.9
.3	2.3	.....	.3	1.3	.....	.....	.....	5.9	5.2
.....	.6	.9	.3	.....	.....	.....	.6	16.0	5.7
3.8	4.3	.2	.5	.....	.....	.2	2.1	20.2	34.9
.....	.6	.....	.....	.....	.....	.7	.....	3.5	2.1
2.9	5.7	.....	.5	.....	.....	.....	.....	8.3	19.1
.....	.....	.....	.....	.....	.....	.....	.....	13.4	38.0
.....	.....	.....	.....	.....	.....	.....	.....	18.7	20.1
.....	.....	.....	.....	.....	.....	.....	.....	33.7	37.0
.....	.....	.....	.....	.....	.....	.....	.....	25.8	29.0
.....	.....	.....	.....	.....	.....	.....	.....	12.3	14.0
.....	.....	.....	.....	.....	.....	.....	.....	9.9	9.0
.....	.....	.....	.....	.....	.....	.....	.....	32.1	10.0
18.1	41.9	4.8	8.2	18.5	21.9	20.5	14.5	426.1	[3] 435.9

[2] Includes 4 man-years on insect control treatments for commodities regulated by plant quarantines.

[3] Includes man-years for all investigational areas, *exclusive of program leadership* which comprises an additional 26.9 man-years.

receive well-justified emphasis.

Research on insect control with conventional insecticides is also revealing new solutions and problems. At the moment, our chemical defenses are besieged by two major forces—insecticidal residues and insect resistance to insecticides.

In view of the overwhelming benefits from insecticide usage and the chaos which would result from abandoning our defenses against disease and hunger, we must do all in our power to maintain our position of strength. This is being accomplished by increased efforts to determine whether or not each chemical adversely affects our total environment. Studies of insecticides in soils and crops are determining the patterns of residue persistence. The NE–36 regional project technical committee (*14*) recently published a bulletin in which were included 79 insecticide residue disappearance curves on various crops.

Similar studies by several State and Federal agencies are being initiated to determine insecticide degradation patterns and residue persistence in air, water, and wildlife. A greatly expanded research effort is needed in developing pesticides whose concentrations in the environment do not increase annually under conditions of normal usage. Studies will have to be accelerated on the effectiveness of insecticides with shorter residual periods through the use of improved formulations and methods of application, and those which may be rendered harmless by natural environmental factors.

Studies are in progress to determine the physiological mechanism of insecticide action. The development of *in vitro* culture of insect cells has provided impetus for this research. The manner of inheritance and the physiological nature of resistance also are under investigation. For example, Metcalf et al. (*13*) are attempting to correlate the relationship of insecticide structure with biological activity. New chemicals with different modes of action also are being evaluated for possible use.

SCOPE OF RESEARCH

Haeussler (*9*) stated that in 1952 injurious insects were costing the United States an estimated $4 billion annually. Presumably this figure has increased in the intervening 12 years. But even on the earlier basis, public investment for entomological research is only a fraction of 1 percent of the estimated annual losses. In 1963 there were about 990 man-years of entomological research in the State agricultural experiment stations and the U.S. Department of Agriculture. Although research scientists in other institutions and in industry are making excellent contributions, we have no estimate available of their research time apportionment.

Research on insects in the USDA is divided between two services. The Forest Service, Division of Forest Protection Research, has 81 scientists who are responsible for research on insect problems in our forests and woodlands. The Agricultural Research Service, Market Quality Research Division, employs 40 entomologists and chemists who perform research on stored products insects. In addition 423 USDA scientists are employed by the Agricultural Research Service, Entomology Research Division, with responsibility for research on insects affecting crops, livestocks, and households. (In 1963 there were also 36 Public Law 480 projects in entomology in foreign countries administered through the ARS.)

The research on insects at the State agricultural experiment stations is usually contained within departmental units. Actually, there are 594 entomologists performing research in the experiment stations. However, part-time teaching, extension, and administrative assignments reduce the actual research effort to an estimated 426 man-years.

Table 1 summarizes current U.S. Department of Agriculture and State experiment station research on the basis of investigational area assignment and type of studies underway on specific commodities. In many instances, Department of Agriculture and State experiment station scientists work cooperatively on problems of regional interest.

In general, studies by entomologists are correlated with the missions of the institutions by which they are employed. In the agricultural experiment stations there is heavy emphasis on basic research in insect biology, nutrition, physiology, and toxicology. This situation probably reflects the close affiliations of the stations with the graduate schools of the land-grant colleges. The major concentration of effort on insecticidal and cultural controls and insect vectors of diseases demonstrates an orientation toward local and regional problems.

There is an approximately equal division of manpower between the stations and the ARS in the areas of apiculture, taxonomy, insecticide analysis,

evaluation and residue determinations, plant resistance to insects, insect pathology, and the evaluation of detection and control equipment.

USDA research is more intensive than that of the States on problems of national or international interest. It includes biological control research, the introduction and evaluation of natural enemies of pests and forest, and stored products insects research. The preponderance of insect control research involving sterility, attractants, and other new techniques is done by Department of Agriculture scientists.

Considering the recent advances and significant trends of the past two decades, one might reasonably assume that entomology is on the verge of even greater discoveries in the immediate future. Unquestionably, advances will be made through entomological research which will have far-reaching implications for other biological and agricultural sciences. As agriculture becomes more intensive, new insect control problems will arise. The tremendous numbers of insects and their remarkable adaptive ability make the control of each damaging species a separate problem. Because of these challenges, the opportunities for entomological ingenuity are limitless.

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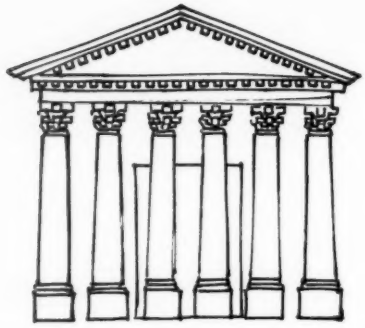

FORUM

Our research financed through agriculture historically has placed heavy emphasis on living things. But these living things have been plants and animals rather than people and families. In the public institutions created and maintained as the "people's colleges," we have had a strong tendency to consider the nonhuman living things as the end rather than as the means for which much broader ends were initially visualized and are currently needed. The balance is still more in favor of guiding bulls and sows rather than people and families who reside in rural areas. This is true both for the amount of information provided and the number of personnel allocated. We provide the sow detailed information on the strata in which she fits and whether she is worth more at Sioux City, Omaha, or Chicago. If she could read she would even find that we have outlined her best route and means of transportation in minute detail. Information to provide decisions on the occupational and geographic orientation of the bull perhaps is even more detailed and extensive. We certainly know his family background better than we know people's families. But we don't have comparable investment and facilities to guide the decisions of families who must remain or move. We should be good to the sows and bulls, but we ought to be equally good to people and families.

On the one hand, we are to be criticized for focusing our main attention on the microaspects of the biological world at the expense of the larger human element. But we also are to be criticized in the social sciences for looking only at the aggregate and "cold resource" side of the human element. When we speak of cutting the labor force in half in agriculture over the next 20 years, the statement is about as inanimate and unrelated to concerns of people as if we referred to cutting the number of tractors by a third. In other words, by extreme focus on either the microaspects of agriculture or the macroaspects of resources and populations, we completely lose sight of the real concerns reflected in the economic and social unit, the family, where the miseries or opportunities of change really are reflected. Here is an important but overly neglected realm of concern in economic development, social change, and agricultural adjustment.

It has been suggested that we need to change the proportions of education and research in our colleges and experiment stations allocated to (*a*) the "material things" involved in consumption, and (*b*) some of the less tangible but more important facets of social change as it relates to growing incomes, increased leisure time, and somewhat increased complexities of a broader consumption framework. Today's housewife can get good supplies and advice on packaged and pre-prepared foods, laundry facilities, and furniture covering from commercial firms, but not on that broader set of sociological, psychological, and economic phenomena which now more nearly serve as the core of her functions.

Little is being done to help individuals make choices in their most important decision areas—for example, families who evaluate the changing economic and social complex about them and remain in farming and rural communities.

Basically, the social and economic unit which must make the crucial decisions of whether to stay in agriculture, to move to other employment and locations, or to follow other alternatives is the family. Even in the case of individual youths who migrate singly to other employment, the first decisions and concerns arise mainly in the family and its particular ties, values, and customs in respect to community and occupation. If society were made up entirely of independent individuals rather than family groups, the moorings and processes of social adjustment to differential economic development and agricultural change would be quite different: the pains and cost of transfer could be much less and the transition would be speeded. The truly complex problems of change and adjustment cer-

tainly surround the family, and it is here that too little attention has been devoted in both research and education.

Our lack of concern with and emphasis on the family aspect of social change, economic adjustment, and agricultural transition has frequently resulted in (*a*) attempts to apply politically inacceptable policies, or (*b*) inabilities to find publicly acceptable policies. Many examples could be cited. Consider first the soil bank, which, if extended far enough, could have solved the farm surplus problem. Yet, it posed the possible evaporation of income and the rapid uprooting of families, especially of nonfarm families in rural communities.

Similarly, the somewhat opposite, or free-market, policy posed for agriculture was never accepted because of its potential or prospective sacrifice to large numbers of farm and nonfarm families located in particular regions of agriculture. It was not the threatened reduction of profits of "mechanical" firms and businesses which caused eventual restraint on the soil bank or the rejection of the free market, but their threatened effect on the income of families and the potentially rapid "prying them loose" from the communities and customs to which they had become deeply attached. Neither was it the impact of these programs on people as individuals, because a society composed only of individuals would have relatively great adaptability and mobility among occupations and locations.

Social change and structural adjustment of agriculture under economic development should not become an end, as seems to be the emphasis in numerous sweeping analyses dealing with labor resources and populations. They should serve as reasons and means for increasing the decision abilities and welfare of families. The processes of adjustment and change can have positive meaning only if they have this accomplishment. In a welfare economics context, more measurements need to be made at the level of the family unit and fewer at the level of either individuals or communities in determining policies, procedures, and institutions which will have positive-sum outcomes. We need to be more certain that we have positive-sum outcomes in the sense that changes implied make all families at least as well or better off (or certainly that the sacrifices stemming from economic growth and social change are at minimum and acceptable level).

If interpersonal comparisons could be made of the distribution of gains and losses stemming from changes of the types posed, we would only need to be certain that the sum of positives for those who gain is greater than the sum of negatives for those who sacrifice. But since we cannot make these interpersonal comparisons of utility changes, our approach to guarantee that the final outcome is postive-sum more nearly has to be that of trying to make all families equal or "better off." This is a tremendous task. But even though we can't be absolutely certain that it is accomplished, recognition of the framework and need leads us in some useful directions in both research and education. At the very minimum, this framework suggests that we can't concentrate all of our attention on nonhuman living things or only on aggregates of labor as a resource or people as a community.

In contrast to the past, we need to be concerned with all families. However, the historic and conventional programs in our land-grant colleges have been directed to persons who could gain from the technical innovations which we "produce and sell" through our research and education. They have almost entirely ignored families squeezed out of agriculture by the process. Certainly one of the major effects of our research and education for technical improvement of agriculture, in crop yields and animals as well as mechanization, has been to reduce labor requirements and squeeze families out of the industry. This is, of course, one of the pains which attach to economic development. But we have too often turned our heads and left stranded the families we have helped to squeeze out. In our positive-sum framework it is just as necessary that we aid the latter families. We have as much obligation to these families, even if they are headed to a different location and occupation, as to those who stay to apply our new innovations, force the structural adjustment of farming, and bring about the exodus of others.

One is impressed with how much we do know about family mobility and the applications of such knowledge which have been made in aiding the large number of families who have had to disappear from the farm landscape. But there are important voids and needs in continuing education directed to the family as a unit, given the fairly firm knowledge we already have.

We have invested very little in trying to gain a

real understanding of the basic interrelationships among important variables and to solve some of the pressing problems of family mobility and family decisionmaking. These two sets of discussions raise serious questions of how well our research and educational resources are allocated to problems of families as compared to problems of other areas so long traditional in colleges of agriculture and home economics. I have no doubt that the problems of allocation are significant ones which should be faced immediately if our research and educational facilities truly have the objective of meeting the urgent problems of people. In the past, we have been more successful in posing the problems than in providing solutions. Yet this is the expected outcome for an area where too few resources have been devoted to research.

In summary, we might pose a very pertinent question: Are we masters or slaves to the complex of social and economic change taking place around us? Considered alone, the family undoubtedly has to take as given the miseries and benefits of this change. But this need not be true of communities and societies, which are made up of families. We have been provided with some excellent guides for action by educational, research, and related institutions. What is important now is that we cast aside the patterns of the past and launch the broadest and most realistic programs of which our resources are capable.

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(Adapted from the author's summary remarks at the Conference on Family Mobility, October 1963, Iowa State University.)

* * *

The Role of Scientific Citations

Editors of science periodicals and publications have long suspected that authors sometimes have other than strictly scientific motives in their choice of literature citations in a research report. Although the primary purpose of a citation list is assignment of credit, other motives are obviously involved. As a result, some lists become excessively long. Critical review papers and theses, particularly, seem to be vulnerable to the practice.

A randomly-selected group of manuscripts submitted for publication by the U.S. Department of Agriculture revealed unnecessary citations in the following categories: (1) Citations dating back to the 18th century, (2) citations of only peripheral concern to the subject, (3) citations supporting universally accepted knowledge, (4) citations inserted mainly to show the depth of the author's library research, and (5) citations designed to foster good relations between the author and his coworkers or his supervisors.

Now, the attitudes and behavior of scientists toward citations will be scrutinized in a research study by the University of Pennsylvania. Supported by funds from the National Science Foundation, the study will include an analysis of the roles of both the technical and sociological aspects of citations in the communication process. The project will be directed by the university's Norman Kaplan, and is designed to test and refine the theoretical framework and the empirical techniques which will best serve to obtain the necessary information. The main research tool will be personal interviews.

As reported in *Scientific Information Notes* (Vol. 6, No. 3, June–July, 1964), emphasis during the interviews will be placed on such items as: (1) Channels of information for each citation, (2) reasons for its inclusion, (3) the point in time at which it was decided to include the item, and (4) alternative citation possibilities that were considered but omitted. Respondents will also be asked about their use of references in reading a scientific paper or seeking information in the literature and their general attitudes toward the use of citations.

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"Ignorance of fundamentals
is a greater obstacle to progress
than lack of a popular appreciation of known facts."

WHITMAN H. JORDAN 1851–1931

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